Temporal Trends in Incidence of Primary Brain Tumours in the Australian Capital Territory and New South Wales 2000 to 2008

A thesis submitted for the degree of Master of Philosophy
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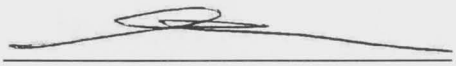
Declaration and Acknowledgements

The work presented here has been compiled in conjunction with the persons listed below, however the majority of this work completed by myself. The resulting papers and presentations have all been prepared personally and according to the advice received from my supervisors. Funding was provided by the The Canberra Hospital Private Practice Research Fund, Canberra, Australia.

I make special mention of my three supervisors, Drs Khurana, Jain and Shadbolt, without whom, the resulting publications and presentations could not have been possible. Their support and guidance has been invaluable and enlightening.



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Abstract

There are conflicting reports from Europe and North America regarding trends in the incidence of primary brain tumour, whereas the incidence of primary brain tumours in Australia is currently unknown.

We aimed to determine primary brain tumour incidence in Australia with age-, sex-, and benign-versus-malignant histology-specific analyses. A multicenter study was performed in the state of New South Wales (NSW) and the Australian Capital Territory (ACT), representing a combined population of >7 million with >97% rate of population retention for medical care.

We retrospectively sourced pathology databases servicing neurosurgical centres in NSW and ACT for histologically confirmed primary brain tumours diagnosed from January 2000 through December 2008. Data were weighted for patient outflow and data completeness. Incidence rates were age standardised and trends analysed using joinpoint analysis.

A weighted total of 7651 primary brain tumours were analysed. The overall US-standardised incidence of primary brain tumours was 11.3 cases 100 000 person-years (+0.13; 95% confidence interval, 9.8–12.3) during the study period with no significant linear increase. A significant increase in primary malignant brain tumours from 2000 to 2008 was observed; this appears to be largely due to an increase in malignant tumour incidence in the ≥65-year age group.

A significant increasing incidence in glioblastoma multiforme (GBM) was observed in the study period (annual percentage change, 2.5; 95% confidence interval, 0.4-4.6, n=2275), particularly after 2006. In GBM patients in the ≥65-year group, significantly increasing incidence for men and women combined (APC, 3.0; 95% CI, 0.5-5.6) and men only (APC, 2.9; 95% CI, 0.1-5.8) were seen. Rising trends in incidence were also seen in meningioma for total male population (APC, 5.3; 95% CI, 2.6-8.1, n=515) and males aged 20-64 years (APC, 6.3; 95% CI, 3.8-8.8). Significantly decreasing incidence trends were observed for Schwannoma for the total study population (APC, -3.5; 95% CI, -7.2 - -0.2, n=492), significant in women (APC, -5.3; 95% CI, -9.9 - -0.5) but not men.

This collection represents the best estimate of primary brain tumour incidence in Australia. Whether the observed increase in malignant primary brain tumours, particularly in persons aged ≥65 years, is due to improved detection, diagnosis, and care delivery or a true change in incidence remains undetermined.

An important trend observed from this study, using benign tumour data collection, was an increasing trend in meningioma and a decreasing trend in Schwannoma in the years 2000 to 2008. This is data for which we have no direct comparison in Australia.

Our registries may observe an increase in malignant tumours in the next few years that they are not detecting now due to late ascertainment. We recommend a direct, uniform and centralized approach to monitoring primary brain tumour incidence, including the introduction of non-malignant tumour data collection.

Examiners Reports

April 5, 2012

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I apologize for the delay in response relative to the thesis of Dr. Martin Dobes and his candidacy for degree of Master of Philosophy. My recommendation is for granting this award and my study copy of the thesis are being sent by DHL Express Courier. My summary supporting this recommendation is necessarily brief but I trust adequate.

In his thesis "Temporal Trends in Incidence of Primary Brain Tumours in the Australian Capital Territory and New South Wales 2000 to 2008", Dr. Dobes clearly demonstrates a compilation of his extensive background study and independent research relative to the epidemiology of brain tumors in the ACT and NSW with comparative data from other nations. The study aims and hypothesis are clearly identified and a study design established for identification of index cases of primary brain tumor. The thesis confirms in detail his diligent attempts to "capture" these cases through retrospective mining of a medical database of the ACT and NSW population. The complexity and magnitude of this undertaking is clearly articulated.

The thesis also identifies and discusses requirement for ethical review, the critical need for accurate pathologic diagnosis, and the monumental tasks of cleaning and weighting raw data. The statistical methodology to establish and identify trends is well appreciated. Dr. Dobes has clearly gained an appreciation for the necessity of collaborations among medical centers for epidemiologic research. The thesis documents some important preliminary data in incidence rate trends for primary brain tumors from the ACT and NSW over the study period. His conclusions stress the importance of a central, national Brain Tumor Registry to provide accurate data for future public health and brain tumor research.

From this review I have complete confidence that Dr. Dobes has accomplished the independent research, made a substantial contribution to learning, and demonstrated the relevance of his research towards better definition of the epidemiology of primary brain tumors in Australia. I am unreserved in my opinion that this work fulfills the thesis requirements for the degree of Master of Philosophy.

This is a detailed study of the incidence of primary brain tumours in Australian Capital Territory and New South Wales. The author summarized the world-wide literature on the incidence of primary brain tumours. This has also highlighted the lack of recent accurate data in Australia.

The method of data collection is exhaustive and well described.

The results of the current study are well described. It is particularly interesting to note the significant increase in incidence of GBM and a rising trend in the incidence in meningioma.

Many factors could have influence the results of the current study. The author discussed in length the various confounding factors. The author presented sound arguments in supporting their assertion of an increasing incidence in GBM.

The author's conclusion of a direct, uniform and centralized approach in monitoring primary brain tumour incidence in Australia is a logical conclusion from his current study.

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Glossary

AAPC - Average Annual Percentage Change

ACT - Australian Capital Territory

AHS – Area Health Service

AIHW - Australian Institute of Health and Welfare

APC – Annual Percentage Change

CBTRUS - Central Brain Tumour Registry of the United States

CCR – New South Wales Central Cancer Registry (managed by the Cancer Institute NSW)

CI - Confidence Interval

CNS - Central Nervous System

CT - Computed Tomography (Imaging)

GBM - Glioblastoma Multiforme

ICD-10 - International Classification of Diseases, 10th Edition

ICD-O - International Classification of Diseases, Oncology

NSW - New South Wales

MR - Magnetic Resonance (Imaging)

US - United States

SNOMED - Systematized Nomenclature of Medicine

SEER - Surveillance, Epidemiology and End Results Program

WHO - World Health Organisation

Preface

Primary brain tumours are an important cause of untimely death in our community, with few risk factors identified to date. Although Australian reports have shown little change in the overall number of new malignant brain tumours per year, overseas studies are showing increases in specific types of brain tumours. We believe this trend may occur here in the next 5–10 years.

Of particular concern to the community is the reported increase in malignant brain tumours that can be fatal in a matter of months, despite best possible treatment. Unique to the brain, unlike other areas of the human body, are slow-growing benign tumours that have potential deleterious effects due to growth in an unyielding enclosed space, i.e., the skull.

Studies, particularly from US and European countries, have focussed on subtype analysis of both benign and malignant brain tumours, and indeed, the US passed a law in 2004 for mandatory reporting of all benign brain tumours.

The current study was commenced in 2008 to address a potential deficit in reliable brain tumour subtype incidence trends in Australian literature. The primary source at that point (and still to this day) of brain tumour data is from state-based cancer registries. Few independent studies have been performed and the Australian literature is scanty at best.

Registry data have reported a stable malignant brain tumour incidence trend, with projections to 2011 remaining at a constant rate. No data on subtypes or benign tumours are available. In reviewing the existing literature, Australia appears to have a real deficit in brain tumour reporting, and it was the aim of this study to set a reliable baseline incidence rate based on brain tumour subtypes with a view for future expansion to a national framework. By following these trends, we may then be able to identify potential risk factors for developing this disease.

Ethical approval was obtained from the ACT Health Human Research Ethics Committee, the NSW Population & Health Services Research Ethics Committee (with lead HREC approval by the NSW Cancer Institute), and the Sydney Adventist Hospital Human Research Ethics Committee to examine the number of new cases per year at the source of definitive diagnosis – i.e. at microscopic analysis in the ACT and NSW regions.

Chapter 1. Introduction

The current study is an ecological multicentre retrospective analysis of histopathological data obtained directly from the source of diagnosis. No associations with risk factors for the development of brain tumours were analysed but the study may be viewed as a pilot for future expansion to a national framework. It has sought to identify the feasibility of such an expansion and addresses a number of perceived deficits in current brain tumour data collection in Australia.

This section describes the current state of literature on the incidence of primary brain tumours both in Australia and overseas, most notably from European and US literature.

It also discusses factors that have influenced the incidence rate over time, particularly the introduction of modern imaging techniques and increased clinical awareness of brain tumours.

Further discussion regarding coding and classification changes are explored in more depth later in the thesis. A brief overview of brain tumours and their subtypes is confined to the appendix.

1.1 Incidence and Descriptive Epidemiology of Primary Brain Tumours

1.1.1 Overview

The incidence of brain tumours is reported to be rising worldwide[1-6] and yet our database searches have so far yielded only limited data published from Australian sources. The most extensive reports about brain tumour incidence to date have come from American[4, 7-12] and European[2, 13, 14] sources.

The recently published 2010 Statistical Report of the Central Brain Tumour Registry of the United States (CBTRUS) provides a primary central nervous system (CNS) tumour age-adjusted incidence of 18.71 cases per 100,000 population in 2006.[10] According to its 2002-2003 Statistical Report,[7] the incidence was 13.4 cases per 100,000 population in 1995. Given that CBTRUS reports CNS tumour incidence age-adjusted to the 2000 US Standard population and that the time period of these reports is well embedded within the MRI era of the US, the observed increase in incidence of approximately 35 - 40% in less than a decade is not likely to be adequately explained by an "ageing population" or by "better diagnosis." If the change is in part due to the effects of delayed reporting or "late ascertainment"[15] from the 15-19 cooperating

state registries used by CBTRUS, it follows that the latest 2010 incidence is also likely to be an underestimation.

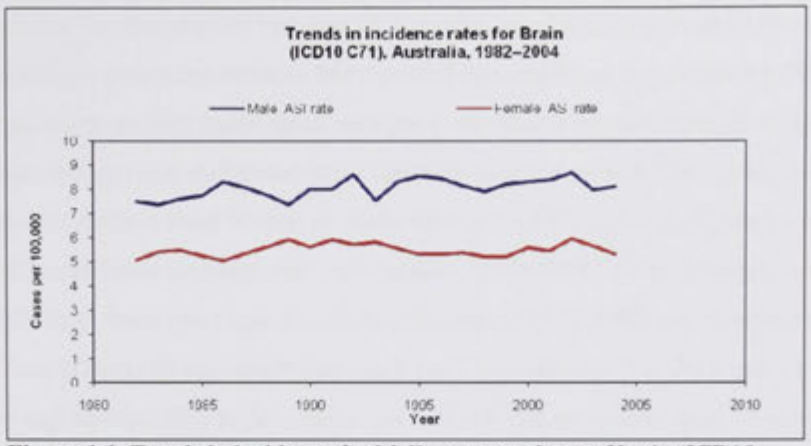


Figure 1.1. Trends in incidence for Malignant neoplasm of brain (ICD10 C71), Australia 1982-2004. Australian Institute of Health and Welfare (AIHW) Australian Cancer Incidence and Mortality (ACIM) book version 1 2007.

Figure 1.1 shows incidence data calculated by the Australian Institute of Health and Welfare (AIHW) for *Malignant neoplasm of brain* (International Classification of Diseases, ICD10 C71) over the period 1982-2004. The incidence represented in the graph above is age-standardised using 2001 Australian census data as the standard population. Surprisingly, little change in the brain tumour incidence rate over 22 years is seen in Australia despite changes in reporting, classification and population demographics.

In the 1970s and 1980s, increased incidence of brain tumours was reported internationally and correlated with use of new imaging technology (CT and MRI)[11, 16, 17] and associated clinical awareness of brain tumours.[2] However, during the mid to late 1990s, when use of CT and MRI technology became widespread in Australia, no such trend in AIHW data is observed. Indeed, a decrease in incidence is observed (particularly for females). Further, changes in brain tumour pathology classification changes also occurred during the reported period 1982-2004 and yet, again, no significant trends are demonstrated in the AIHW data depicted in **Figure 1.1**.

Notably, incidence data (e.g. AIHW data) have tended to include only malignant neoplasms of brain (ICD10 C71), and thus excluded meningioma, pituitary and pineal tumours, acoustic neuroma, and previously, low-grade astrocytoma.[18, 19] Exclusion of these tumours produces a tendency to underestimate incidence as well as undervaluing the importance of benign brain tumours. Australia is unique when compared to the US in that there is legislated *total coverage* of malignant brain tumour data collection, whereas the US uses "*sample methodology*" for its incidence estimates.

In Australia, a small number of descriptive epidemiologic studies on primary central nervous system (CNS) tumours were published in series from Melbourne, Tasmania and Adelaide[20-24] from the early 1990s. One Victorian study[20] of 4,577 tumours showed age- standardised incidence rates for malignant CNS tumours of 5·0 cases per 100,000 person-years males and 3·4 cases per 100,000 person-years females but reported no significant trends during the period 1986-1988 regarding specific histological subtypes. Another Victorian study[21] analysed 3,575 cases of primary benign and malignant brain tumours over the period 1982-1990 with no clear trend in incidence, while a third Victorian study reported a 14% non-significant increase in childhood malignant brain tumours over two decades 1970-1989.[24] The Tasmanian study[22] analysed 1,752 cases from two registries during the period 1978-1992 and reported increasing age-standardised primary brain cancer incidence rates in males (16.3 to 26.2 cases per 100,000 person-years) and females (9.7 to 18.0 cases per 100,000 person-years) aged 75+, most prominent in cases of glioblastoma multiforme (GBM). The Adelaide study[23] was a short study of a low sample population, showing an increased risk of glioma in women who reported working with cathode-ray tubes.

Our literature searches have to date yielded no comparable Australian studies published subsequently.

1.1.2 Overseas Literature

Descriptive epidemiology relies largely on population-based cancer registries, which record cases according to the International Classification of Diseases for Oncology (ICD-O), which corresponds closely to the WHO Classification of Tumours of the Central Nervous System. Often, incidence data include only malignant neoplasms and thus exclude most meningiomas and, previously, also low-grade astrocytomas.[19]

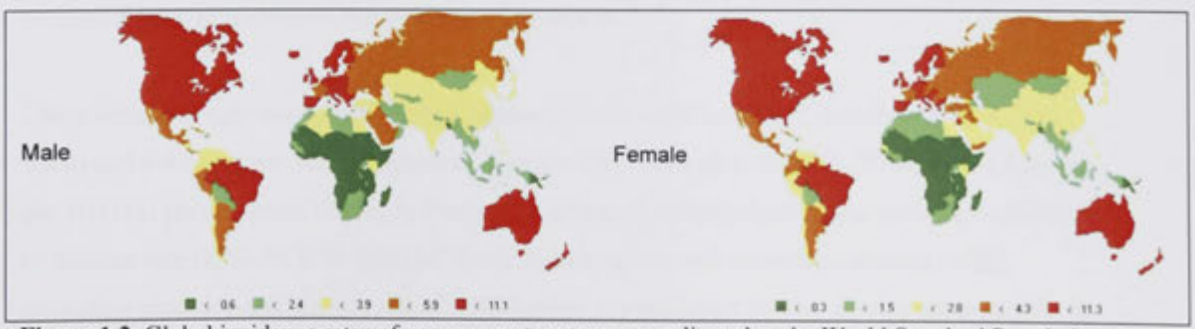


Figure 1.2. Global incidence rates of nervous system tumours, adjusted to the World Standard Population (all ages; cases per 100,000 persons per year). Rates tend to be higher in highly developed countries.[19]

As seen in **Figure 1.2**, age-adjusted brain tumour incidence rates tend to be higher in highly developed countries. This likely reflects more diligent monitoring/reporting practice and health care delivery but an underlying organic cause needs to be considered as well.

In western Europe, North America, and Australia, there are about 6.0 -11.0 new cases of primary intra-cranial tumours (including meningiomas) cases per 100,000 population per year in men and 4.0 -11.0 new cases in women.[19, 25-27] Europe and North America provide the most comprehensive data to date and are explored in greater detail below.

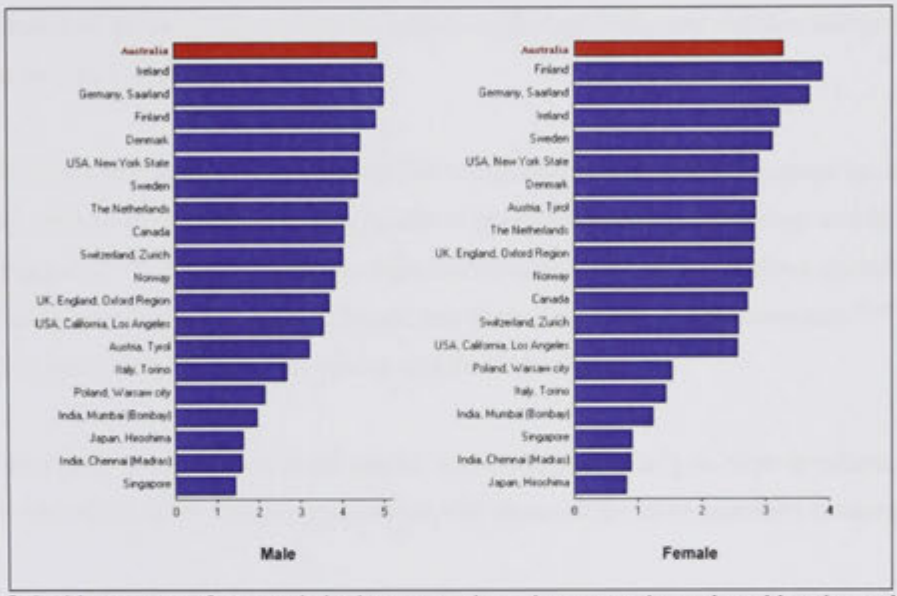


Figure 1.3. Incidence rates of astrocytic brain tumours in various countries and world regions adjusted to the World Standard Population (all ages; cases per 100,000 person- years).[19]
Australian rates are approximations based on NSW Central Cancer Registry data (these are not part of the original figure).[28]

A population-based study of primary brain tumours in Kumamoto prefecture suggests that, in Japan, gliomas are about half as frequent as in the US but that childhood tumours are at similar rates to Western countries.[29-33] As seen in **Figure 1.3**, Asian populations generally show lower incidence rates of astrocytic tumours that Caucasians.[19, 26]

China describes age-standardised rates (adjusted to the world standard population) of 4.2 (in 2000) and 4.4 cases per 100,000 person-years (in 2005) in males, and 3.1 (2000) and 3.3 cases per 100,000 person-years (2005) in females.[34] Although not specified, these data were collected by tumour site (ICD-10, C70-72) and likely include spinal and metastatic disease, while excluding pituitary and pineal tumours. No further comparable Chinese studies are available in our search of English literature.

New Zealand has published incidence rates of intra-cranial neoplasm with particular focus on socioeconomic factors and race. One early study discussed a substantial difference in brain tumour incidence rates in non-Maori vs. Maori populations over a 40 year period,[35] but a recent study has suggested no difference.[36] The latest study quotes an age-adjusted incidence rate of high grade glioma of ~4.0 cases per 100,000 person-years and the authors suggest an improved capture rate of Maori tumours explains their observations.

Between 1995 and 2009, 439 males and 383 females had primary intra-cranial tumours in Kuwait with only a statistically significant declining trend described for medulloblastoma. The study included all primary intra-cranial neoplasms including malignant and non-malignant entities as well as metastatic disease.[37]

In the 1980s and 1990s, there was considerable worldwide interest in brain tumour incidence with many authors attributing increasing trends to improved imaging technology and better clinical diagnosis,[2, 12, 38] but some studies reported increases irrespective of these changes.[39]. A reported increase of approximately 1-2% per year in the incidence or brain tumours,[35, 40] particularly in the elderly,[11, 22, 41] but also in children[42] was seen.

There is now renewed interest in brain tumour incidence, particularly in more developed countries, and much of the current presentation will focus on the more pertinent contemporary studies.

United States of America

The largest collection of brain tumour incidence data comes from multiple databases compiled by the Central Brain Tumour Registry of the United States (CBTRUS), established in 1992. From that time, only malignant cases of brain tumours were reported, but in January 2004, with the passage of the Benign Brain Tumour Cancer Registries Amendment Act (Public Law 107-260), all cancer surveillance registries expanded their primary brain tumour collection to include tumours of benign and uncertain behaviour.

CBTRUS contains data collected from the National Program of Cancer Registries (NPCR) and states belonging to the National Cancer Institutes Surveillance, Epidemiology and End Results (SEER) program. Initially, data from 12 state registries across the US were included in the 2002-3 report, covering data from 1995-1999. In the latest 2010 report, 47 population–based cancer registries were included.

Tables 1.1 and 1.2 show reported incidence rates for sequential CBTRUS reports for all primary CNS tumours, as well as for selected histologies. These trends, although appearing to be increasing each year, need to be interpreted with caution in view of the number of participating registries with each report. That is, in the earlier reports, fewer registries were available to contribute data than in the later reports. As such, incidence rates are not directly comparable between reports. Changes in incidence within and between years have been attributed by CBTRUS mainly to better surveillance and delayed reporting (late ascertainment).[10, 15]

	CBTRUS Report				
Diagnosis Year	**2002-2003**	**2004-2005**	**2005-2006**	**2007-2008**	**2010**
1995	13.4				
1996	14				
1997	14.2	13.5			
1998	14.5	13.9	14.2		
1999	14	14.1	14.5		
2000		14.2	14.8	15.2	
2001		14.7	15.3	15.9	
2002			15.2	16.2	
2003				17	
2004				18.2	
2005					
2006					18.71

Table 1.1. Age-adjusted incidence of primary CNS tumours in the sequential reports of CBTRUS. Adapted from Khurana et al.[43]
Incidence is the number of cases per 100,000 population age-adjusted to the US population 2000 standard.

The CBTRUS data series is an internationally recognised resource for brain tumour incidence data. They have a comprehensive coverage of all types of primary brain tumours from an increasing number of participating registries.

Most US studies have been published from the CBTRUS/SEER data series,[4, 15, 17, 18, 44-46] but a few have come from individual population-based registries.[47-50] Most recently however, studies rely more heavily on CBTRUS data and use it as the gold standard. A few of the more widely cited US studies from the last 10-20 years include the following.

Hoffman and colleagues demonstrated only modest overall increases in brain tumour incidence rates in a study of CBTRUS data spanning the period 1985-1999.[4] However, the authors reported increasing incidence in both microscopically-confirmed and non-confirmed meningiomas and nerve sheath tumours. An observation suggesting that the increases were less likely to be due to improvements in diagnosis and highlighting the importance of continued collection of meningioma and nerve sheath tumour (benign brain tumour) data to explain the trends.[4]

A similar study published in the same year (2006) from many of the same authors, analysed the incidence of vestibular Schwannoma (a nerve sheath tumour of the eighth cranial nerve) from the CBTRUS and Los Angeles cancer databases. They demonstrated increasing incidence of both nerve sheath tumours overall and of vestibular Schwannoma, again, suggesting continuing monitoring of these tumours to be important.[46]

McCarthy and colleagues have recently (2008) described increasing trends in oligodendroglial tumour incidence corresponding to decreases in astrocytic tumour incidence over the same period (1992-2004). The suggestion from the authors is that misclassification and improvements in molecular diagnostics and treatment have lead to the observed change.[18]

Table 1.2 below shows compiled data from sequential CBTRUS reports to give the reader an idea of incidence rates cases per 100,000 persons per year. The latest report was released at the end of 2010 and includes data for the years 2004-6.

		CBTRUS Report				
	Tumour	**2002-2003** 1995-1999 data	**2004-2005** 1997-2001 data	**2005-2006** 1998-2002 data	**2007-2008** 2000-4 data	**2010** 2004-6 data
Total	Glioblastoma	3.24	3.01	3.05	3.09	3.17
	Meningioma	3.86	4.18	4.52	5.35	6.29
	Nerve Sheath	1.05	1.11	1.17	1.46	1.61
	Pituitary	0.92	0.82	0.92	1.37	2.40
	Total	**14.02**	**14.10**	**14.80**	**16.52**	**18.71**
Male	Glioblastoma	4.02	3.75	3.86	3.94	3.97
	Meningioma	2.46	2.57	2.75	3.17	3.76
	Nerve Sheath	1.07	1.12	1.19	1.48	1.63
	Pituitary	1.00	0.85	0.94	1.37	2.31
	Total	**14.22**	**13.92**	**14.50**	**15.77**	**17.44**
Female	Glioblastoma	2.59	2.40	2.39	2.38	2.51
	Meningioma	5.04	5.56	6.01	7.19	8.44
	Nerve Sheath	1.04	1.11	1.17	1.45	1.60
	Pituitary	0.88	0.82	0.93	1.42	2.56
	Total	**13.86**	**14.27**	**15.07**	**17.19**	**19.88**

Table 1.2. Age-adjusted incidence of selected primary CNS tumours in the sequential reports of CBTRUS by gender. Adapted from Khurana et al.[43] Rates are expressed in cases per 100,000 person-years.

The current study has used CBTRUS data as its primary point of comparison to US incidence rates and many of the quoted rates have been standardised to the 2000 US standard population for ease of comparison. Methodology used has also been modelled on the most recent publications from the CBTRUS database.[4, 18, 46]

Europe

Europe is unique in its brain tumour data collection with a number of countries having mandatory collection of both malignant and non-malignant tumours for their entire population, some from birth. Denmark, Finland, Norway, and Sweden have well developed brain tumour registries that include notifications for all residents from two independent sources, clinicians and pathologists, ensuring a high completeness of coverage. These registries also cover cases without microscopic or radiological confirmation and tumours detected at autopsy.[16]

Two studies from the four Nordic countries mentioned showed a stable, even declining incidence of adult intracerebral tumours over the period 1969-98 and 1974-2003. Increases in incidence were observed in the 1970s and 1980s, coinciding with improved diagnostic methods, and largely confined to the elderly.[16, 51] Meningioma incidence from the same four countries from 1968-1997 showed a significant increase, more strongly in women than men aged 35-59. The increase coincides with the introduction of CT imaging technology but is accompanied by a decrease in post-mortem diagnoses. The authors suggest a hormonal influence for the observed increase (e.g. use of hormone replacement therapy in the period).[52]

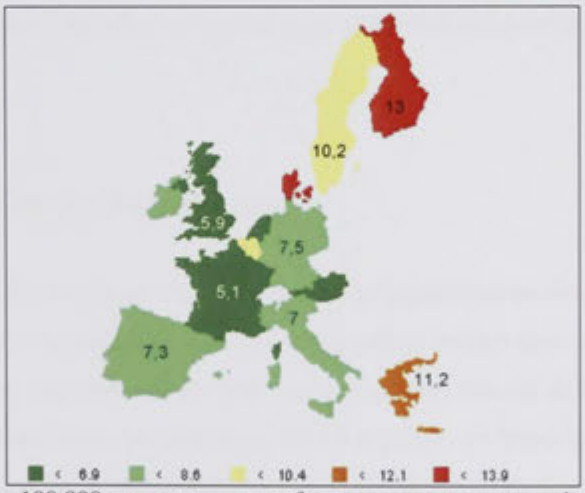


Figure 1.4. Incidence per 100,000 persons per year of nervous system tumours in Europe, adjusted to the European Standard Population. Cancer in the European Union (1995), IARC, 1999.[19]

		England	Wales	Scotland	Northern Ireland	UK
Numbers	Males	2092	159	196	81	2528
	Females	1529	136	165	37	1867
	Persons	3,621	295	361	118	4395
Age standardised rates*	Males	8.3	10.1	7.6	10.4	8.4
	Females	5.3	7.6	5.2	4.4	5.4
	Persons	6.8	8.8	6.3	7.2	6.8
95% confidence intervals	Males	(8.0 to 8.7)	(8.5 to 11.7)	(6.5 to 8.6)	(8.1 to 12.7)	(8.1 to 8.7)
	Females	(5.1 to 5.6)	(6.4 to 8.9)	(4.4 to 6.0)	(3.0 to 5.8)	(5.2 to 5.7)
	Persons	(6.5 to 7.0)	(7.8 to 9.8)	(5.6 to 6.9)	(5.9 to 8.5)	(6.6 to 7.0)

*Directly age standardised (European) rate per 100000 population at risk.
Source: www.cancerresearchUK.org

Table 1.3. Brain and central nervous system tumours: UK incidence 1999. Taken from McKinney 2004.[47]

Figure 1.4 and **Table 1.3** show summary brain tumour incidence rates for Europe and the UK.[19, 47] From the map, it can be seen that incidence rates are subject to geographical variation, a finding confirmed by a number of other European studies, even within a similar area (**Table 1.3**).[19, 47, 53]

In Austria, a recent change in brain tumour collection occurred with the setting up of the Austrian Brain Tumour Registry that was set up under the auspices of the Austrian Society of Neuropathology for the registration of both malignant and non-malignant tumours. The template used was based on the 2004 US experience and published (2009) incidence rates are comparable to the CBTRUS database with overall age-adjusted rates of 18.1 cases per 100,000 person-years that were higher in females (18.6/100,000) than males (17.8/100,000).[54]

Studies from Europe have now turned their focus to risk association to attempt to explain rising brain tumour incidence trends with particular focus on mobile phone technology.[43, 55-59] This is of course beyond the scope of the current study, and beyond reach in Australian, but I mention it to describe current trends in brain tumour incidence reporting internationally (the US appears to also be following suit[60]).

A future direction for Australia may involve setting up similar nation-wide databases and risk association studies.

1.1.3 Australian Cancer Registry data

In Australia, CNS tumour incidence data is collected by population-based cancer registries, some of which include non-malignant tumours, while others restrict data collection to malignant disease.[20] Further, some registries collect both malignant brain tumour data as well as tumours with malignant *behaviour* but a non-malignant WHO *grading*. An important distinction. This is a feature of the NSW and ACT cancer registries and is explored in further detail below as a point of divergence from the current study's definition.

Few independent studies or reviews on brain tumour incidence have been published from Australia recently, but a review by Giles in 1995 gives a good historic picture of malignant brain tumour incidence. Giles quotes age-standardised incidence rates at that time of 6.6 and 4.9 cases per 100,000 person-years in males and females respectively. Incidence rates 1982-1991 by histological type are shown in **Table 1.4** below.

	MALES		FEMALES	
	Number	Rate	Number	Rate
Glioblastoma multiforme	662	2.80	462	1.83
Astrocytoma	372	1.73	274	1.29
Medulloblastoma	51	0.31	21	0.12
Oligodendroglioma	33	0.14	21	0.09
Ependymoma	30	0.15	29	0.16
Other glioma	106	0.46	86	0.38
Meningioma	302	1.27	665	2.69
Nerve sheath tumour	80	0.35	83	0.35
Other specified type	41	0.20	46	0.21
Unspecified type	10	0.05	2	0.01
Not microscopically confirmed	363	1.47	379	1.28
TOTAL	2052	8.91	2068	8.40

Table 1.4. CNS tumour incidence by histological type: age-standardised rates per 100,000 population, Victoria, Australia 1982-1991. Source, Victorian Cancer Registry. Taken from Giles 1995.[61]

Since 1972, public health legislation in NSW requires that all new cases of malignant brain tumours are notified. From 1986 to 2004, the NSW Central Cancer Registry (CCR) was based at the NSW Cancer Council and received notifications under the authority of the Public Health Act of 1991. Since 2004, it has been based at the NSW Cancer Institute.

The NSW CCR collects notifications of malignant neoplasms from public and private hospitals, departments of radiation oncology, nursing homes, pathology laboratories, outpatient departments and day procedure centres. Notifications are also received from other state- and territory-based cancer registries.

NSW is the most populous state of Australia with 6,888,014 residents in 2007. According to the Australian Bureau of Statistics publication of the Estimated Resident Population in June 2006 for NSW, the population increased by 70,832 people between 2006 and 2007.[62]

From the latest NSW CCR publication, the Australian standardised (to the Australian 2001 population) incidence rates for brain cancer in 2007 were 8.3 and 5.2 cases per 100,000 person-years respectively in males and females, with an 84-86% histological verification rate. In 2009 and longer term (up to 2021), the estimated incidence rates are estimated to remain at 2007 levels with 8.0 cases per 100,000 person-years in males and 5.4 in females.[63] Between 1998 and 2007, incidence rates of brain cancer showed no statistically significant change in males and females (see **Figure 1.5**).[62]

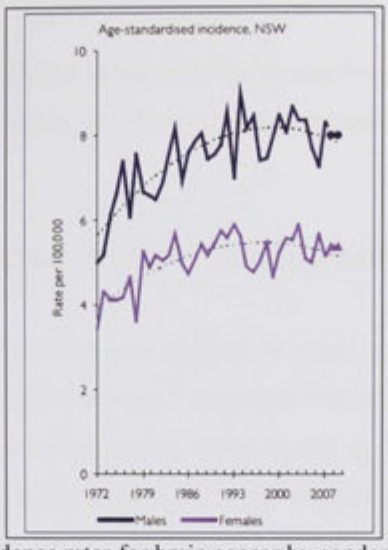
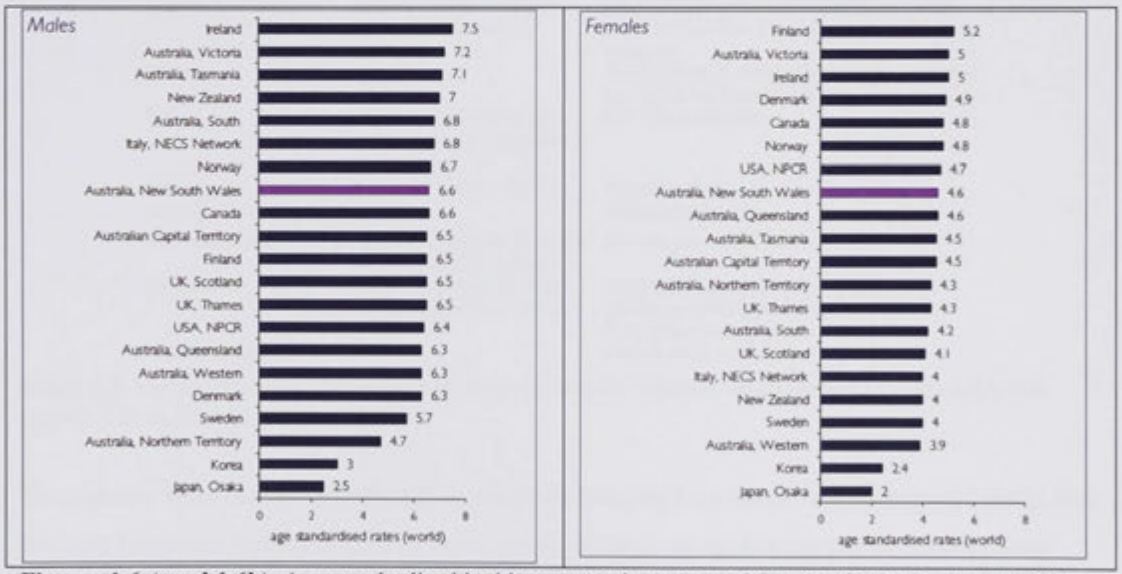


Figure 1.5. Age-standardised incidence rates for brain cancer by gender in NSW 1972-2007.[62]

Figures 1.6a) and 1.6b) show comparative age-standardised incidence rates in males and females for brain cancer for the years 1998-2002 between NSW and other registries from Australia and overseas.[28]



Figures 1.6a) and 1.6b). Age standardised incidence rates in males and females for brain cancer 1998-2002.[64]

The data presented above from the NSW CCR summarise the current state of malignant brain tumour collection in Australia over the years 1972-2007. No significant changes have been reported in the years 1998-2007.

We view the Australian Registries as the gold standard in Australia for brain tumour collection. Their collection encompasses tumours of malignant and uncertain behaviour and notifications are received from multiple different sources in fully identified format, allowing accurate control for representation and migration (something beyond the scope of the current study's resources).

No benign brain tumours are included in the NSW CCR data however. This is the main point of divergence between the current study and the established collection of the registry.

1.2 Risk Factors Associated with the Development of CNS Tumours

Risk factors associated with the development of brain tumours analysed in the international literature have included an ageing population,[39] constitutional factors (female hormones,[65] genetic predispositions[66, 67]), environmental exposures (ionizing radiation, mobile phone technology,[16, 43, 55-59, 68-71] radiotherapy in children[72]) and various others (see **Table 1.5** below).

Factor	Specific aspects	Evaluation of risk
Ionising radiation	Therapeutic, diagnostic	Therapeutic doses increase risk but diagnostic x rays do not appear to be associated
Mobile phones	Radiofrequency exposure	Current epidemiological and biological evidence does not support any link between mobile use and the risk of brain tumours
Extremely low frequency electromagnetic fields	Residential and occupational exposure	Little consistent evidence but research is ongoing
Specific infections	Viruses, *Toxoplasma gondii*, in utero influenza and varicella	No candidate viruses consistently associated or found in tumour tissue. Few links to in utero exposure
Allergies	Atopy	The presence of atopy appears to be protective but further work needed to identify mechanisms
Diet	Nitrosamine/nitrosamide/ nitrite/nitrate consumption. Aspartame	No consistent evidence
Tobacco	Cigarettes, cigars, pipes	No associations
Alcohol		No associations
Chemical agents	Hair dyes, solvents, pesticides, traffic related air pollution	No consistent evidence
Occupations	Rubber manufacture, vinyl chloride, petroleum refining	Small risks associated with working in the petroleum/oil industry but no mechanism or specific chemical known
Head trauma/injury		No consistent evidence

Table 1.5. Summary of environmental risk factors for brain tumours investigated in epidemiological studies. Taken from McKinney 2004.[47]

To examine these factors specifically at this time is beyond the scope of the proposed study, but they are important factors to bear in mind, particularly given increasing public concern over mobile phone usage[16, 43, 55-59, 69-71, 73] and "electropollution".[74]

1.3 Aims and Hypothesis

- Measure a better estimate of brain **tumour burden** in the ACT and NSW populations to provide essential information to policy makers;
- Establish a **baseline incidence rate** for any future monitoring of changes in incidence, because this may allow early intervention in the context of potential environmental causes;
- Collect and present reliable data on age-adjusted, histologically specific, sex-differentiated incidence data on both benign and malignant brain tumours;
- Determine a better estimate of age-adjusted incidence, trends and annual percentage change for selected histologies of brain tumours in the ACT and NSW over the period 1994 – 2008.
    - Specifically, **test the hypothesis that the age-adjusted incidence rate of *astrocytoma, acoustic neuroma and meningioma* in the ACT and NSW is increasing**;
- Identify any gaps in current collection of data that would assist further investigation of brain cancer in the ACT and NSW; and
- Facilitate dissemination of data for public education and ongoing research purposes.

1.4 Ethical Approval

Ethical approval was granted for the study by the following bodies;

- ACT Health Human Research Ethics Committee
- NSW Population & Health Services Research Ethics Committee with lead HREC approval by the NSW Cancer Institute
- Sydney Adventist Hospital Human Research Ethics Committee

Approval was granted by the NSW Population & Health Services Research Ethics Committee for a multicentre study into the incidence of primary brain tumours for the years 1994-2008 at the following sites in NSW;

- John Hunter Hospital
- Royal North Shore Hospital
- Prince of Wales Hospital
- Wollongong Hospital

- St Vincent's Hospital Darlinghurst
- Concord Repatriation General Hospital
- Liverpool Hospital
- Royal Prince Alfred Hospital
- Nepean Hospital
- Westmead Hospital
- The Children's Hospital at Westmead
- Sydney Adventist Hospital
- Douglass Hanly Moir Pathology, Macquarie Park, Sydney
- Dalcross Private Hospital

Data collection was approved for the following parameters

- All primary brain tumours (malignant and benign) including cranial nerve tumours
- In the time period January 1994 to December 2008
- Histological description (e.g. ICD-O-3, SNOMed III)
- Topographical location (e.g. ICD-O-3, ICD 10)
- Date of diagnosis
- All age groups
- Both male and female
- Year of birth
- Postcode

The approval process for this project extended from July 2008 until February 2009, with the ACT Health Human Research Ethics Committee granting approval on the 21 July 2008 and the NSW Cancer Institute HREC granting approval on th 17 February 2009 (see **Appendix 6.8** for approval letters).

Please consider the length of a 64-page NSW Health On–line National Ethics Application Form (NEAF) and 19-page Site Specific Assessment Form (SSA) at www.neaf.gov.au. Now consider 21 such forms (both NEAF and SSA) needing to be completed online, sent to the 21 participating sites for signatures and then sent in triplicate to the NSW Cancer Insitute HREC for approval. Furthermore, separate private hospital ethical approval (e.g. Sydney Adventist Hospital) was also required. This was a time consuming task and seemed out of proportion to the simple nature of the study.

Unfortunately, approval for the use of fully identified data was not granted - a significant issue for ensuring an accurate case capture rate. Without the use of identifiers, data were not able to be analysed across multiple different collection centres, and representations of the one patient to a number of different centres would thus presumably be included in the analysis. This would lead to an over-estimation of the incidence rate.

Moreover, when approached to complete a data match for the study, our Cancer Registries were too short staffed, and the authors were referred to a private data matching service. Data matching is the accessing of fully identified Cancer Registry data and performing a cross match with an independent study's results. The fee for the private data matching service was beyond the budget of the current study. Again, this is a significant issue for ensuring an accurate case capture rate. Without the aid of a data matching service, we have no yardstick by which to compare our data.

Although the above point would regardless be true of all benign brain tumours since these data are not currently collected, data matching for malignant tumours would provide a good indication of our data quality.

Overall, ethics approval proved a very time consuming process. This process would benefit from review, particularly if future studies similar to the current one are to be performed.

In the end, complete data sets for all participating centres from mid-1999 to December 31 2008 were obtained.

1.5 Sampling

The study population was defined as all histologically confirmed primary brain tumours from patients with listed ACT or NSW postcodes.

The ACT/NSW region was used as the sample population because of its low rate of outward migration based on cross-border patient flows from the Australian Institute of Health and Welfare Hospital Separation data.

Initial analysis of ACT data in isolation highlighted this issue, where cross border flows between the ACT and NSW were highly significant, resulting in poor case coverage. Additionally, it was found that The Canberra Hospital (ACT) incidence rates were heavily affected by operating rates and service delivery (see *1.5.2 Migration Effect* below).

Later in the study, our data collection encompassed the largest stereotactic radiosurgery centre in the ACT/NSW region – the Prince of Wales Cancer Centre. This centre treats meningiomas, pituitary adenomas and vestibular Schwannomas either as the primary treatment option or as an adjuvant to surgical treatment.

Stereotactic radiosurgery is often employed for brain tumours where the risk of surgery outweighs the benefit such as in skull base tumours or tumours in eloquent areas of the brain. Capture of this data has added to the completeness of our data set, particularly in terms of the benign brain tumours listed above.

1.5.1 Coverage

Fifteen pathology units servicing all 25 neurosurgical hospitals in the ACT and NSW regions of Australia provided data on all incident primary brain tumours diagnosed in the period 1994 to 2008.

Capture of brain tumours at this level allowed greater diagnostic accuracy.

Cancer Registries and previous independent studies have included non-operative brain tumour diagnoses as well as tumours diagnosed at autopsy.[75] Although this approach yields large sample sizes, the current study aimed to provide a greater acuity in assessment of histological subtypes that is lost upon inclusion of tumours diagnosed solely on imaging technology, conservative (i.e. non-operative) treatment or clinical decision making.

Importantly, pathology data is the primary point of diagnosis, and provides the most up to date information on histology, topography and time of diagnosis.

Other sources have argued that the timing of diagnosis should be based upon the date of first *clinical* diagnosis.[53, 75] This approach is justified in those tumours that are either inoperable or slow growing and thus allows capture of a greater number of tumours, particularly those that are followed with a "wait-and-watch" approach. However, notification systems employed by Registries in this regard are subject to significant reporting delay and require resources beyond the scope of the current study.

The European Network of Cancer Registries has developed a hierarchy regarding the date of diagnosis.[76] In order of declining priority;

1. Date of first histological or cytological confirmation of this malignancy (with the exception of histology or cytology at autopsy). This date should be, in the following order:
    a. date when the specimen was taken (biopsy)
    b. date of receipt by the pathologist
    c. date of the pathology report.
2. Date of admission to the hospital because of this malignancy.
3. When evaluated at an outpatient clinic only: date of first consultation at the outpatient clinic because of this malignancy.
4. Date of diagnosis, other than 1, 2 or 3.
5. Date of death, if no information is available other than the fact that the patient has died because of a malignancy.
6. Date of death, if the malignancy is discovered at autopsy.

Coverage of brain tumours diagnosed in the ACT/NSW region has been assumed to be complete in the study period, but capture of brain tumours diagnosed at smaller private pathology units cannot be excluded.

1.5.2 Migration effect

Migration of patients between states for health care can have an undue effect on the incidence rate, particularly when no control for outward migration exists (as in the current study). The Australian Cancer Registries have an agreement where fully identified data is shared between states and territories in order to control and quantify this migration.

Within Australia there is no direct quarterly measure of interstate migration, unlike that of natural increase and net overseas migration. Instead, quarterly estimates of interstate migration are modelled using Medicare change of address data. This model is reviewed and updated every five years using data from the latest Census of Population and Housing.[77] Statistics published by the Australian Bureau of Statistics record the number of interstate arrivals and departures. In the period March 2000 to September 2008, the median population for arrivals into NSW was 21849 persons and 4751 persons for the ACT, while the median population for departures was 28048 persons and 4752 persons.[78, 79] Population flows into and out-of the ACT/NSW region have thus remained relatively stable over the study period.

Unfortunately, as noted, the lack of ethical approval for the use of identified data and the reluctance for data matching by our local registries, have made full control for migration an insurmountable issue in light our resource capabilities. Consequently, an average weighting of 3.21%, calculated from both public and private Australian hospital separation data (2006-7), was applied to the data to account for patient outflow from the study region.[80] Inflows were controlled for by manual exclusion of postcode of residence. To account for completeness of data as well as migration effect an overall average weighting of 5.00% was used.

To highlight the issue, a preliminary analysis of incidence trends using data only from The Canberra Hospital was performed while awaiting NSW ethical approval and data. The data was of top quality owing to dedicated staff and all codes were cross-checked by professional coders at The Canberra Hospital. A pictorial representation of our methods is shown below (**Figure 1.7**) where all tumours operated within the ACT were refined by exclusion of irrelevant diagnoses, recurrence of a tumour in the same patient, and patients residing in an area outside the ACT.

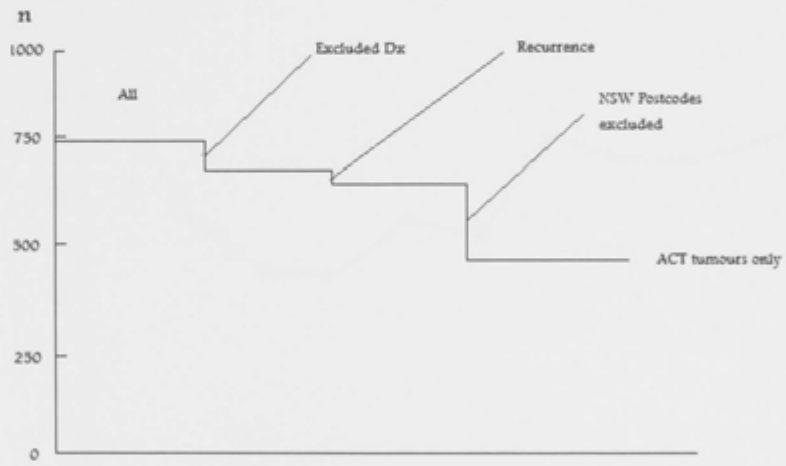


Figure 1.7. A pictorial representation of our preliminary analysis of all primary brain tumours operated in the Australian Capital Territory in the years 1997-2008 with refinement of numbers based on diagnosis, recurrence and postcode. Final number = 427.

A crude incidence rate of ~11.0 – 12.0 cases per 100,000 person-years was calculated over the years 1997-2008. The analysis was limited by the low number of tumours (n=427). A decrease in the age-standardised incidence rate of primary brain tumours is observed in the years 1998-2000 (**Figure 1.8**). This trend over time however was biased by migration out of the territory reflected by operating rates over the time period (**Figure 1.9**). This reflected the strong influence of health service delivery on The Canberra Hospital neurosurgical service in terms of access to health care and referrals to other centres outside the ACT.

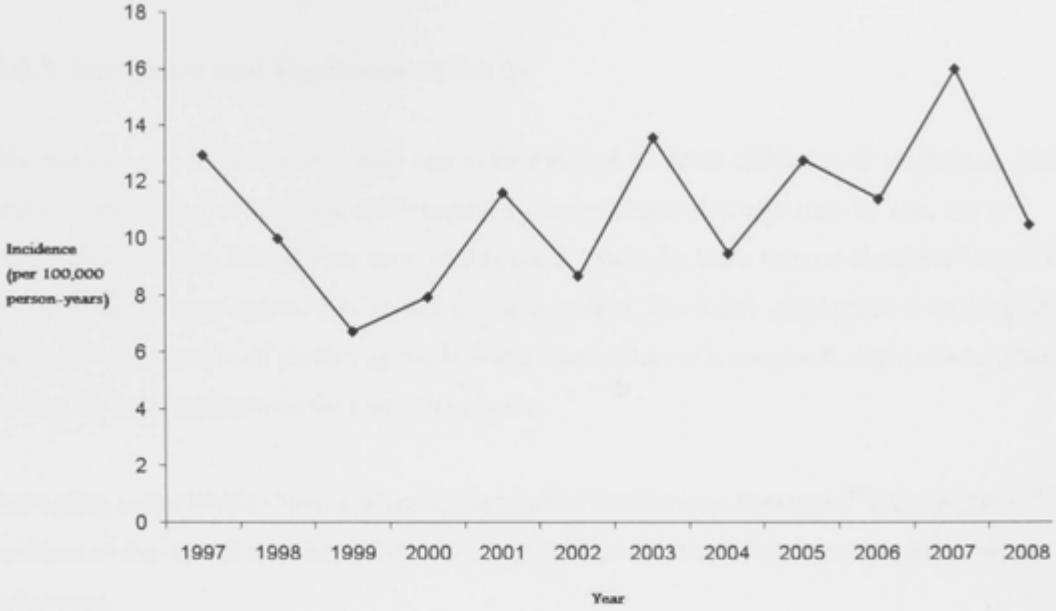


Figure 1.8. Incidence of all primary brain tumours in the ACT, adjusted to the Australian Standard Population as at census 2006 by 5 year age groupings, per 100,000 person-years, 1997-2008

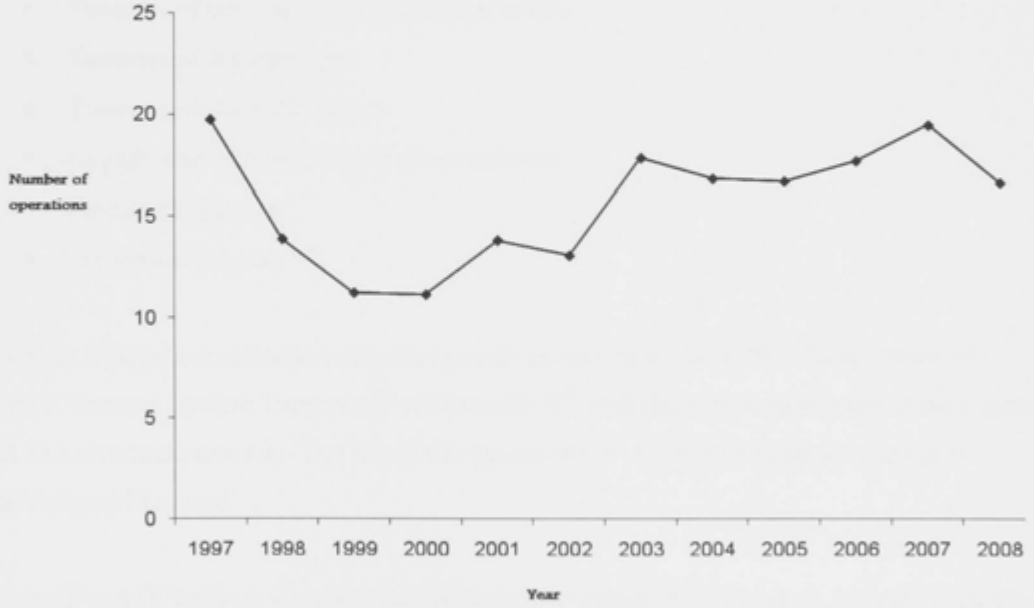


Figure 1.9. Number of operations by year for all (ACT and other Australian states) primary brain tumours at The Canberra Hospital by number in the period 1997-2008.

Further analysis was suspended until receipt of NSW data, which, as discussed above, has a very low outward migration rate for health care. Moreover, the ACT and NSW region is a very homogenous population covering multiple ethnicities, backgrounds and exposures, and thus an ideal area to analyse the trends in brain tumour incidence.

1.5.3 Inclusion and Exclusion criteria

The primary aim of the current study was to establish an accurate collection of all primary intra-cranial tumours in the ACT and NSW region by examining trends over time by age, sex and histological subtype. Perhaps the most widely used system for brain tumour classification is the World Health Organisation (WHO) classification system. The histological grade defined under this system is a means of predicting the biological behaviour of a neoplasm, with tumour grade having clinical implications for treatment choice.

According to the WHO Classification of Tumours of the Nervous System (4th Edition 2007),[81] tumours of the central nervous system may be classified into the following major histological subgroups:

- Tumours of neuroepithelial tissue
- Tumours of the cranial and paraspinal nerves
- Tumours of the meninges
- Tumours of the sellar region
- Lymphomas and haematopoietic neoplasms
- Germ cell tumours
- Metastatic tumours

We have defined our collection of brain tumours according to the WHO Classification of Central Nervous System Tumours 4th edition (2007)[82] with the exclusion of extra-cranial, germ cell and metastatic tumours. The use of this system allows greater comparison of rates in international literature.

Grade III and IV tumours demonstrate histological evidence of malignancy, including nuclear atypia, brisk mitotic activity and necrosis, with invariably fatal outcomes. Grade I lesions are generally considered tumours of low proliferative potential and the possibility of cure with surgical resection alone. Lesions designated grade II are typically infiltrative in nature, and despite low proliferative activity, often recur. Some grade II tumours tend to progress to higher grade tumours, for example, low-grade diffuse astrocytomas that transform to anaplastic astrocytoma and glioblastoma.[83] These tumours are thus assigned an uncertain or borderline behaviour code (/3), despite being grade II classification. This is the basis of brain tumour collection by the Australian Cancer Registries, who collect all malignant and borderline tumours for "brain" (ICD code C71). Collection of these tumours is mandated by Australian law and

published rates are thus considered only in terms of "malignant" tumours, with no collection of benign or non-malignant tumours.

Unlike the Australian Cancer Registries however, we have defined malignant brain tumours as WHO Grade III and IV. Grade II tumours are considered a separate entity in the current study that despite having the potential to progress to malignancy, are considered non-malignant at the time of diagnosis. Combining both borderline and malignant brain tumours into the one incidence rate creates difficulty in comparison of published rates in the literature, as well as being less meaningful clinically. This is particularly true considering no recent published data exists on histological subtypes or benign tumours in Australia.

Registry data also includes collection of systemic lymphoma, metastatic, extracerebral, soft tissue and germ cell tumours (see **Table 1.6**).[62] Collection of this data was beyond the scope of the current project - spinal, metastatic tumours and lymphoma have origins outside the central nervous system. Interestingly, there are multiple diagnoses not traditionally considered either brain tumours or malignant tumours in the list, and may explain the higher numbers of tumours observed by the registry compared to the current study (see **Chapter 2**).

C71	Brain (ICD-O-2 C71) From codes	1	Tumours of neuroepithelial tissue	8680, 9360-9362, 9364, 9380-9506, 9520-9523
		1.1	Gliomas	9380-9384, 9391-9460, 9480, 9481
		1.11	Astrocytic tumours	9384, 9400-9421, 9424, 9440-9442, 9481
		1.12	Oligodendroglial tumours and mixed gliomas	9382, 9450-9451
		1.13	Ependymal tumours	9383, 9391-9394
		1.14	Gliomas of uncertain origin	9380, 9381, 9422, 9423, 9430, 9460, 9480
		1.2	Embryonal tumours	9470-9473, 9490, 9500-9504
		1.21	Medulloblastoma	9470-9472, 9364, 9473 (site: C716, C717)
		1.22	Other embryonal tumours	9490, 9500-9504, 9364, 9473 (other sites than C716, C717)
		1.31	Choroid plexus tumours	9390
		1.32	Neuronal & mixed neuronal glial tumours	8680, 9491, 9505, 9506, 9520-9523
		1.33	Olfactory tumours	9520-9523 (site C300)
		1.34	Pineal parenchymal tumours	9360-9362, 9364, 9473 (site C753)
		2	Tumours of cranial nerves	9540-9570
		3.1	Meningioma	9530-9535, 9537, 9538
		3.2	Soft tissue	8800-9044, 9120-9142, 9150, 9536, 9539, 9160-9251
		3.3	Melanoma	8720-8790
		4.1	Germinoma	9060, 9064
		4.2	Other germ cell	9070-9072, 9080-9085, 9100, 9101
		5.1	Pituitary tumours	8140-8381 (site C751)
		5.2	Craniopharyngioma	9350
		6	Other specified tumour	8050-8650, 8693-, 8710, 9270-9330, 9370-9371, 9580-9581
		7	Unspecified tumour	8000-8045
		9	Other, very odd	else
C71	Brain (ICD-O-2 C71) From VIC		Glioblastoma	9440-9442
			Astrocytoma	9384, 9400-9421, 9430, 9424
			Other gliomas	9470-9473, 9450-9460, 9391-9394, 9380-9383, 9390-9394, 9480
			No histological confirmation	999, 0, 800

Table 1.6. Histology codes collected by the NSW CCR classified using IARC histological groupings.[62]

Of the mesenchymal brain tumours, only haemangioma and haemangiopericytoma were included in the study. Pituitary, craniopharyngeal duct and pineal tumours, as well as primary

central nervous system lymphoma and cranial nerve tumours were included in the analysis. Atypical teratoid/rhabdoid tumours were also included in the study – being the main differential diagnosis of medulloblastoma.

Tumours in patients from overseas or other Australian states and territories were excluded from the analysis. This exclusion was based on listed postcode from the pathology report that was not verified as a patient's place of residence.

To capture the tumours described above, pre-existing search engines at each site or specifically written search programs were employed to capture related diagnoses (see **Tables 1.7 and 1.8**). Methods varied from site to site depending on available technology with a broad margin of irrelevant diagnoses initially being included. These were then refined at the co-ordinating centre (The Canberra Hospital) by a limited number of investigators to maximise consistency of methods.

C70.0 Cerebral meninges
C70.1 Spinal meninges
C70.9 Meninges unspecified
C71.0 Cerebrum
C71.1 Frontal lobe
C71.2 Temporal lobe
C71.3 Parietal lobe
C71.4 Occipital lobe
C71.5 Cerebral ventricle
C71.6 Cerebellum
C71.7 Brain stem
C71.8 Overlapping lesion of brain
C71.9 Brain unspecified
C72.0 Spinal cord
C72.1 Cauda equina
C72.2 Olfactory nerve
C72.3 Optic nerve
C72.4 Acoustic nerve
C72.5 Other and unspecified cranial nerves
C72.8 Overlapping lesion of brain and other parts of central nervous system
C72.9 Central nervous system, unspecified
C75.1 Pituitary gland
C75.2 Craniopharyngeal duct
C75.3 Pineal gland

Table 1.7. Topography Codes for Brain Tumours (ICD 10 Malignant Codes).

M 9421/1 Pilocytic astrocytoma
M 9425/3 Pilomyxoid astrocytoma
M 9424/3 Pleomorphic xanthoastrocytoma
M 9384/1 Subependymal giant cell astrocytoma (Tuberous sclerosis)
M 9400/3 Diffuse Astrocytoma
M 9420/3 Fibrillary astrocytoma
M 9411/3 Gemistocytic astrocytoma
M 9410/3 Protoplasmic astrocytoma
M 9401/3 Anaplastic astrocytoma
M 9440/3 Glioblastoma
M 9441/3 Giant cell glioblastoma
M 9442/3 Gliosarcoma
M 9381/3 Gliomatosis cerebri
M 9450/3 Oligodendroglioma
M 9451/3 Anaplastic oligodendroglioma
M 9382/3 Oligo-astrocytoma
M 9382/3 Anaplastic oligo-astrocytoma
M 9383/1 Subependymoma
M 9394/1 Myxopapillary ependymoma
M 9391/3 Ependymoma
M 9391/3 Cellular Ependymoma
M 9393/3 Papillary Ependymoma
M 9391/3 Clear cell Ependymoma
M 9391/3 Tanycytic Ependymoma
M 9392/3 Anaplastic ependymoma
M 9390/0 Choroid plexus papilloma
M 9390/1 Atypical choroid plexus papilloma
M 9390/3 Choroid plexus carcinoma
M 9430/3 Astroblastoma
M 9444/1 Chordoid glioma of the 3rd Ventricle
M 9431/1 Angiocentric glioma
M 9493/0 Dysplastic gangliocytoma of cerebellum (Lhermitte-Duclos)
M 9412/1 Desmoplastic infantile astrocytoma /ganglioglioma
M 9413/0 Dysembryoplastic neuroepithelial tumour
M 9492/0 Gangliocytoma
M 9505/1 Ganglioglioma
M 9505/3 Anaplastic ganglioglioma
M 9506/1 Central neurocytoma
M 9506/1 Cerebellar neurolipocytoma
M 9509/1 Papillary glioneuronal tumour
M 9509/1 Rosette-forming glioneuronal tumour of the fourth ventricle
M 9361/1 Pineocytoma
M 9362/3 Pineal parenchymal tumour of intermediate differentiation
M 9362/3 Pineoblastoma
M 9395/3 Papillary tumour of the pineal region
M 9470/3 Medulloblastoma
M 9471/3 Desmoplastic nodular medulloblastoma
M 9471/3 Medulloblastoma with extensive nodularity
M 9474/3 Anaplastic medulloblastoma
M 9474/3 Large cell medulloblastoma
M 9473/3 CNS primitive neuroectodermal tumours (PNETs)
M 9500/3 CNS Neuroblastoma
M 9490/3 Ganglioneuroblastoma
M 9501/3 Medulloepithelioma
M 9392/3 Ependymoblastoma
M 9560/0 Schwannoma (Neurilemoma, Neurinoma)
M 9560/0 Cellular Schwannoma
M 9560/0 Plexiform Schwannoma

M 9560/0 Melanotic Schwannoma
M 9540/0 Neurofibroma
M 9550/0 Plexiform
M 9571/0 Perineurioma, NOS
M 9571/3 Malignant perineurioma
M 9540/3 Epithelioid MPNST
M 9540/3 MPNST with mesenchymal differentiation
M 9540/3 Melanotic MPNST
M 9540/3 MPNST with glandular differentiation
M 9530/0 Meningioma
M 9531/0 Meningothelial meningioma
M 9532/0 Fibrous (fibroblastic) meningioma
M 9537/0 Transitional (mixed) meningioma
M 9533/0 Psammomatous meningioma
M 9534/0 Angiomatous meningioma
M 9530/0 Microcystic meningioma
M 9530/0 Secretory meningioma
M 9530/0 Lymphoplasmacyte-rich meningioma
M 9530/0 Metaplastic meningioma
M 9538/1 Clear cell meningioma
M 9538/1 Chordoid meningioma
M 9539/1 Atypical meningioma
M 9538/3 Papillary meningioma
M 9538/3 Rhabdoid meningioma
M 9530/3 Anaplastic (malignant) meningioma
M 9120/0 Haemangioma
M 9133/1 Epithelioid haemangioendothelioma
M 9150/1 Hemangiopericytoma
M 9150/3 Anaplastic hemangiopericytoma
M 9364/3 Ewing sarcoma - PNET
M 9161/1 Haemangioblastoma
M 9590/3 Primary CNS lymphoma
M 9350/1 Craniopharyngioma
M 9351/1 Adamantinomatous Craniopharyngioma
M 9352/1 Papillary Craniopharyngioma
M 9582/0 Granular cell tumour
M 9432/1 Pituicytoma
M 9400/1 Astrocytoma low-grade, NOS
M 9400/3 Astrocytoma high-grade, NOS
M 9380/1 Glioma low-grade, NOS
M 9380/3 Glioma high-grade, NOS
M 8272/3 Pituitary carcinoma
M 8140/0 Adenoma, NOS

Table 1.8. Example of Morphology Codes for Brain Tumours (ICD-O, SNOMed III).

Discrepancies in data completeness were followed up with the collecting institution and if further specific searches did not yield more complete data, the records were excluded from the analysis.

1.5.4 Recurrence/representation

If not done manually, a random number was assigned to the names of patients to control for repeat presentations to the same hospital/hospital network. Data quality was to be assessed through data matching of fully identified data with Cancer Registry data. However, ethical approval for this undertaking was not granted and due to staff shortage issues, the registries were unable to match data for all malignant tumours.

This was a significant issue for quality assurance, particularly because there is no mandatory reporting of benign tumours in Australia. Data matching of malignant data may have given at least some indication of the quality of benign tumour data. No control for repeat presentations of one patient to multiple hospitals (not in the same network) was performed. This gives rise to the potential for overestimation of the incidence rate.

1.6 Database Background, Design and Search Method

Thirteen sites participated in the current study. Most sites employed on-site search engines to identify cases through SNOMED morphology and topography codes. Extraction and translation of data to an excel spreadsheet for the larger centres (RPAH, RNSH, STVH, POW) was computerised. A number of the smaller centres however, required a very labour-intensive method of manual translation from individual pathology reports (after computerised identification of cases). The following provides an overview of the methods employed at each site including the period of data received and primary search method.

Collecting Centre	Database (year)	Search Method	Translation to Excel
The Canberra Hospital (public and private)	1996 – 2009 (mid)	Text diagnosis**	Manual
Sydney Adventist Hospital	2008 – 2009 (mid)	Text diagnosis**	Manual
St Vincent's Hospital (public and private)	1994 – 2009 (mid) Postcodes by manual extraction	SNOMED*	Manual
Prince of Wales Hospital (public and private) including St George Hospital (public and private)	1999 – 2008	SNOMED*	Computerised
Children's Hospital at Westmead	1997 – 2008	Text diagnosis**	Manual
John Hunter Hospital	1994 – 2008	SNOMED*	Computerised
Wollongong Hospital	2000 – 2008	SNOMED*	Manual
Nepean Hospital	1994 – 2008 Two databases Postcodes by manual extraction	SNOMED*	Manual
Royal North Shore Hospital Including North Shore Private, Royal North Shore Hospital (public), Dalcross Private Hospital, Clinical Cancer Registry, Royal North Shore Pathology Meeting data collection, Dr Janice Brewer private records	1975 – 2009 (mid) Multiple databases sourced and amalgamated	SNOMED*	Computerised
Westmead Hospital (public and private)	1996 – 2008	SNOMED*	Manual
Douglass Hanly Moir Pathology	1987 – 2009 (mid) Four separate databases	SNOMED*	Manual
Royal Prince Alfred Hospital database including Concord Repatriation General Hospital and Liverpool Hospital	1994 – 2008	SNOMED* Specific search program written on-site	Computerised
Prince of Wales Cancer Centre	1970 – 2008	Text diagnosis**	Computerised

Table 1.9. Database information including collecting site, years of data coverage, search method and method of translation to excel.
SNOMED topography (T) and morphology (M) code search. T-A (brain), TB1* (pituitary), T-B2* (pineal), T-91* (pituitary), M-91*, M-93*, M-94*, M-95* codes were used over two versions of SNOMED (international 3.5, and II). * means a wildcard search
**Text diagnosis using keywords; glioma, brain, tumour, pituitary, astrocytoma, cancer, CNS, Schwannoma, vestibular Schwannoma, acoustic neuroma, adenoma, meningioma, ependymoma, haemangioblastoma, medulloblastoma, neuroblastoma, oligodendroglioma, oligoastrocytoma and pineal

The data range of the current study was limited by data received from the Prince of Wales Hospital, which provided data from mid-1999 to end-2008. This centre contributed approximately 15% of all tumours to the current collection (see **Chapter 3**), and so analysis of trends prior to the year 2000 would have been unreliable, with a large margin for error.

1.7 Effect of Individual Hospital Coding Practice on Capture Rate

Databases are used by hospitals to generate statistics for quality care and resource management but coding practice varies between hospitals depending on the training and experience of coders. The majority of hospital coding practice follows the International Classification of Diseases (ICD) coding system that has been in its 10th edition (ICD-10) since 1994. Since 1996, yearly updates to the ICD-10 have been published, and the time to widespread use of updates varies between hospitals. Additionally, because of the vast list of available codes (topographical and morphological) and multiple different methods of coding the same tumour, standard practice varies between institutions.

Routine search methods can thus lead to variability of capture rate of brain tumours. For this reason, we employed an on-site data collector familiar with the system after discussion with on-site pathologists to work out the optimal search method to maximise capture rate of brain tumours. For example, topographical vs. morphological vs. text diagnosis search method. Specifically, brain tumours fall into the ICD-O (oncology) coding system that is currently in its 3rd edition (ICD-O-3). Examples of important corrections to the early edition of ICD-O-3 include re-classification of pilocytic astrocytoma from a malignant entity (/3 behaviour) to a borderline/uncertain tumour (/1 behaviour). Rhabdoid meningiomas were reclassified in the same year (2001) from /1 to /3 behaviour code. The ICD system is related but distinct from the Systematized Nomenclature of Medicine (SNOMED) employed by most pathology units in the ACT/NSW region. The SNOMED system has a greater number of tumour codes and is thought to be more specific to histological diagnosis than the ICD system. We have thus employed the SNOMED coding system for the present study and converted each code to its equivalent WHO 2007 code. For the purposes of the current study however, the differences between the three systems are minimal.

Widespread use of a particular coding system or use of an updated code varies between hospitals and was thus an important issue to clarify prior to commencing a search to ensure near complete capture rates. In terms of the current study, specific searches were needed to capture pituitary and pineal tumours, which, depending on the site, could have potentially been missed if only the "brain" or "pituitary/pineal" topography code was used.

These coding issues are significant for maintenance of accurate databases but coding changes for brain tumours in the years 2000-2008 are minimal, and the present study has remained relatively unaffected by coding changes. Further, we have re-coded all tumours according to the latest WHO classification for morphology and ICD classification for topography to avoid this issue. The issue is worth highlighting to make the reader aware that caution is needed when interpreting the data. We cannot guarantee complete capture rates and coding issues are a large contributor to missed tumours. We have attempted to minimise this error through tailoring our searches to the on-site capabilities of the databases.

1.8 Central Database Management (The Canberra Hospital)

This section outlines the methods used to combine, sort, code, clean and analyse the dataset. Strict methodology is important when handling large volumes of data to minimise error and maximise consistency.

1.8.1 Combining Data

De-identified data were received at the central site (The Canberra Hospital) via electronic transfer of an Excel spreadsheet. All diagnoses were coded to SNOMED morphology and ICD 10 topography coding systems (see **Tables 1.7 and 1.8**) by a limited number of investigators to maximise consistency of coding practice. Professional coders at The Canberra Hospital were employed to cross-check the coding method.

1.8.2 Cleaning Data

~12,200 records were received to the central site. Data were cleaned by individual Excel spreadsheet by site prior to amalgamating all relevant data into one spreadsheet. A pictorial representation of the cleaning and weighting process is provided below (**Figure 1.10**).

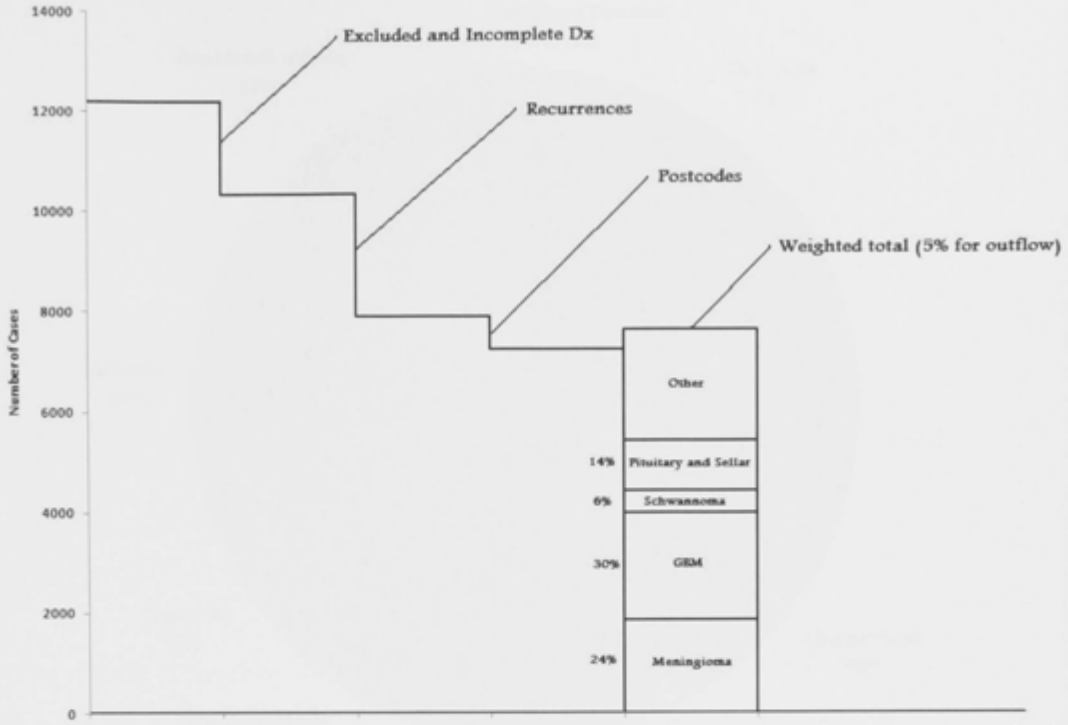


Figure 1.10. A pictorial representation of the cleaning and weighting process used in the current study. A breakdown of major tumour subtypes is also provided.

As mentioned previously, each collection site employed a different search method to extract records from the local database and so the quality of data also varied between sites. If a record was ambiguous or incomplete, a further check with the site was performed for additional information based on a unique code for that entry. If the additional search did not yield adequate information, the entry was discarded. Common examples included topographical site of meningioma (intra-cranial versus extra-cranial), not-otherwise-specified (NOS) codes, date of birth, and postcode.

Commonly encountered irrelevant diagnoses included lymphoma, metastatic disease, extra-cerebral tumours, abscess and infection ($n \approx 1800$). Patients with recorded postcodes from overseas or outside of the ACT/NSW region ($n \approx 450$) were excluded from the analysis.

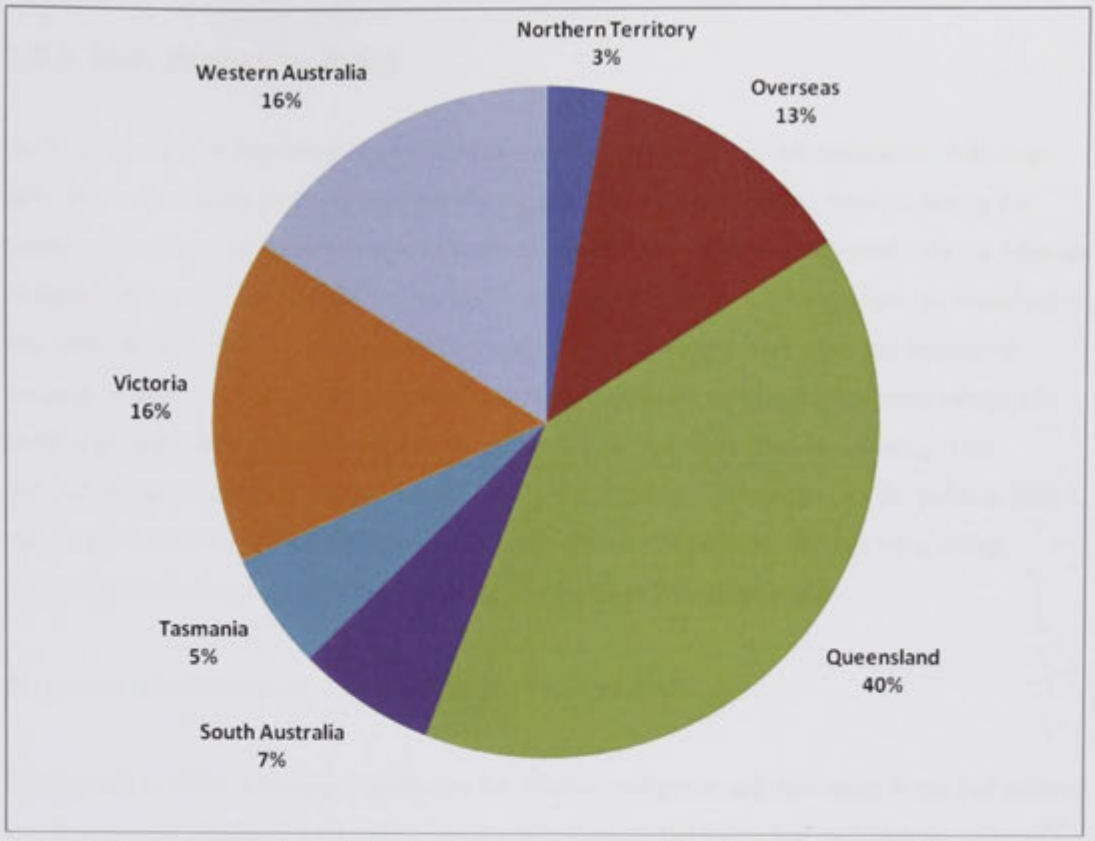


Figure 1.11. Distribution of postcodes for patients excluded from the analysis (n = 450 total).

49 records were excluded from the analysis based on incomplete data fields. The incomplete fields included lack of date of diagnosis, date of birth, gender, unspecified site and uncertain diagnosis, the most common of which was lack of date of diagnosis.

Recurrence of a tumour in a patient was defined as the same histological subtype of brain tumour occurring in that patient two months or more after initial resection. If two entries were found for the one patient within two months of each other, with the same histological diagnosis, the entries were assumed to be the same tumour and only the earliest record was included for analysis ($n \approx 1350$ excluded). If the two entries were greater than two months apart and of the same histological diagnosis, the later entry was excluded as being a recurrence of the first tumour ($n \approx 1100$).

This definition is still under debate and applies only for malignant tumour collection in the United States, with some suggesting the need for a longer timeframe (e.g. four months or one year) for recurrence.[84] This issue is related but also distinct from the Rule of Multiple Primaries (see below).

1.8.3 Data Reporting Rules

Coding rules are an important aspect of data collection in incidence determination. Although affecting only a small proportion of the whole, the rules deserve special mention due to the potential bias that variation amongst definitions might cause. This is particularly true in relation to brain tumours. In the early 20th Century, neurosurgeon Harvey Cushing made the observation that some brain tumours are malignant because of their histology, and some are malignant because of their location. Despite advances in technology and treatment, this observation still holds true, with slow growing tumours in eloquent (i.e. vital to normal functioning) and difficult-to-access areas of the brain still having significant consequences for the patient. Brain tumours, whether benign or malignant, can cause devastating effects through mass effect, oedema, haemorrhage, or seizures, resulting in a similar clinical outcome.

No current world standard of coding rules has been published.

On January 1, 2004, a standard collection for all non-malignant and malignant brain and central nervous system tumours in the United States according to the following sites was developed.[85] Of note, anatomically, the tentorium cerebelli is a dural structure that separates the cerebellum from the cerebrum. The hypothalamus, pallium and thalamus are classified as infratentorial structures but yet are anatomically located superior to the tentorium and incisura tentorii (opening of the tentorium that transmits the cerebral peduncles)!

Cerebral Meninges			
ICD-O-3	Term		
C70.0	Cerebral meninges		
C70.1	Spinal meninges		
C70.9	Meninges, NOS		
Brain			
		Supratentorial	Infratentorial
C71.0	Cerebrum	X	
	Basal ganglia	X	
	Central white matter	X	
	Cerebral cortex	X	
	Cerebral hemisphere	X	
	Corpus striatum	X	
	Globus pallidus	X	
	Hypothalamus		X
	Insula	X	
	Internal capsule	X	
	Island of Reil	X	
	Operculum	X	
	Pallium		X
	Putamen	X	

	Rhinencephalon	X	
	Supratentorial brain, NOS	X	
	Thalamus		X
C71.1	Frontal lobe		
C71.2	Temporal lobe		
	Hippocampus		
	Uncus		
C71.3	Parietal lobe		
C71.4	Occipital lobe		
C71.5	Ventricle, NOS*		
	Cerebral ventricle		
	Choroid plexus, NOS*		
	Choroid plexus of lateral ventricle	X	
	Choroid plexus of third ventricle	X	
	Ependyma*		
	Lateral ventricle, NOS	X	
	Third ventricle, NOS	X	
C71.6	Cerebellum, NOS		X
	Cerebellopontine angle		X
	Vermis of cerebellum		X
C71.7	Brain stem		X
	Cerebral peduncle		X
	Basis pedunculi		X
	Choroid plexus of fourth ventricle		X
	Fourth ventricle, NOS		X
	Infratentorial brain, NOS		X
	Medulla oblongata		X
	Midbrain		X
	Olive		X
	Pons		X
	Pyramid		X
C71.8	Overlapping lesion of brain		
	Corpus callosum	X	
	Tapetum	X	
C71.9	Brain, NOS*		
	Intra-cranial site*		
	Cranial fossa, NOS*		
	Anterior cranial fossa	X	
	Middle cranial fossa	X	
	Posterior cranial fossa		X
	Suprasellar	X	
Spinal Cord and Other Central Nervous System			
C72.0	Spinal cord		
C72.1	Cauda equina		
C72.2	Olfactory nerve		
C72.3	Optic nerve		
C72.4	Acoustic nerve		
C72.5	Cranial nerve, NOS		
C72.8	Overlapping lesion of brain and central nervous system		
C72.9	Nervous system, NOS		

Table 1.10. Topographic sites used for coding based on clinical information supplied on pathology forms in the current study. Taken from SEER coding advice.[85]

The impetus for this definition was the Benign Brain Tumour Cancer Registries Amendment Act (Public Law 107, 260) and has been used in the current study (**Table 1.10).**

The following section details some of the more penitent rules for coding of benign, borderline and malignant brain and CNS tumours applicable to the current study. For further details, the National Program of Cancer Registries (NPCR)[86] and SEER Websites[85], the 2009 Facility Oncology Registry Data Standards publication,[87] the 2004 Centres for Disease Control and Prevention publication[84] and the 2007 National Cancer Institute Surveillance Epidemiology and End Results Program publication,[88] the 2002 North America Association of Central Cancer Registries publication[89] should be referred to.

As mentioned, on January 1, 2004, all cancer registrars in the United States were mandated by Public Law 107, 260, the Benign Brain Tumour Cancer Registries Amendment Act to collect benign brain and central nervous system tumours.

The reason for reporting benign and borderline brain and CNS tumours are:

- Benign and borderline CNS tumours cause disruption in normal function similar to that caused by malignant CNS tumours.
- Location of a CNS tumour is as important as tumour behaviour (benign or malignant) for morbidity and mortality.[85]

Benign Tumour Rules

1. Pilocytic astrocytoma changed from malignant behaviour (/3) to borderline behaviour (/1) when the 3rd edition of the ICD-O was published. Registrars in the United States were instructed to continue to assign the code with malignant behaviour. However, we have instead coded these tumours as non-malignant tumours, an important point of divergence from US practice.
2. Where a diagnosis of Schwannoma has been made in an intra-cranial site with no further detail, the tumour was coded to "C72.5 Cranial nerve, NOS". The site of intra-cranial Schwannoma (9560/0) can be difficult to determine and not always available from pathology reports. If the site was indeterminate, the tumour was excluded from the analysis.
3. A benign meningioma with the site listed as skull should be coded to the cerebral meninges. The meninges are between the skull and the intra-cranial tissues. A meningioma would originate in the meninges and can invade the skull. Meningioma arising strictly from bone is rare.
4. Orbital meningiomas were excluded from the study if not involving the sphenoid bone.

5. Classification of meningioma subtypes is still relatively difficult to define at the histological level. Where doubt existed regarding subtype, the tumour was first coded to the highest grade, and then to the diagnosis of the highest M code (see **Table 1.8**).
6. Chondroma (9220/0) is a benign tumour of cartilage cells. These tumours are not currently reportable tumours in the United States and have not been included in the current study.
7. Chordoma is a malignant tumour arising from the embryonic notochord, and chondrosarcoma (9220/3) is a malignant tumour of cartilage cells. Although these tumours are reportable in the United States (if their site is intra-cranial) they have not been included in the current study.

Malignant Brain Tumour Rules

1. Where doubt regarding diagnosis exists, tumours were coded to the **highest grade.**
2. Where the text diagnosis is given as St Anne Mayo Grade II Astrocytoma, the tumour was classified as "Astrocytoma, Not Otherwise Specified".
3. Where the text diagnosis is given as Grade 4 (of 4) Glioma, the tumour was classified as "9440/3 Glioblastoma, NOS".
4. Where the topography code for a tumour was "not-otherwise-specified" and no further information regarding its intra- or extra-cerebral location was found, the entry was excluded from the analysis.
5. A high grade glioma or astrocytoma, if not otherwise specified, was coded to "M 9380/3 Glioma high-grade, NOS" and "M 9400/3 Astrocytoma high-grade, NOS" respectively. Similarly with low grade glioma and astrocytoma.

Rules for Multiple Primaries

For large scale cancer registries, determining whether multiple tumours in the same patient are two separate entities or a recurrence of the first tumour is a significant issue. The problem is compounded by the volume of notifications from multiple different sources received by the registries.

Multiple primary tumours may be considered generally as either synchronous, in which the cancers occur at the same time (the SEER definition is within 2 months); and (2) metachronous, in which the cancers follow in sequence (more than 2 months apart) (see **Figure 1.12**).[89]

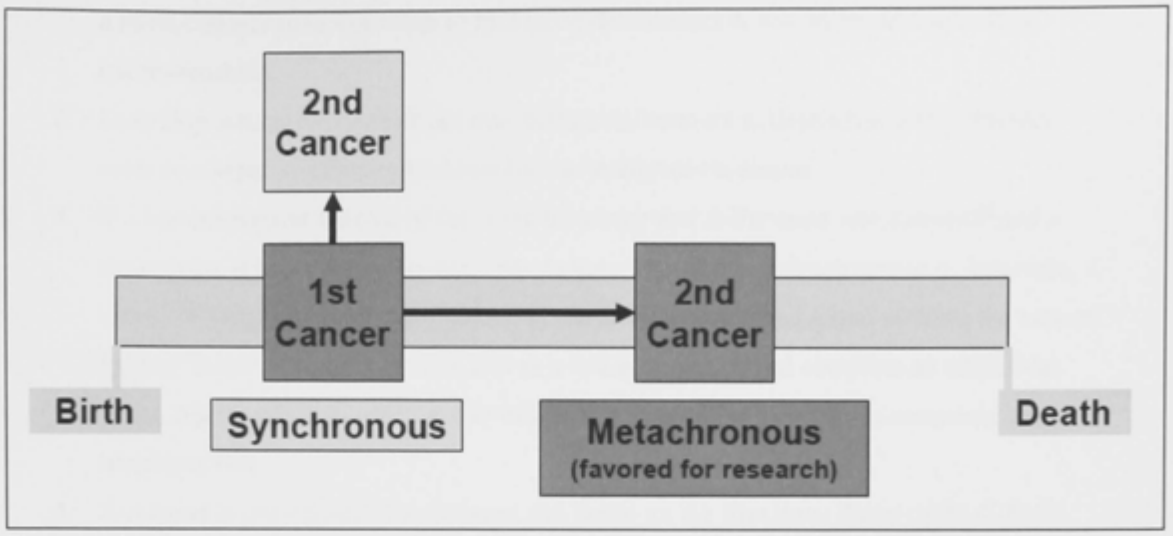


Figure 1.12. Pictorial represntation of synchronous and metachronous tumours. Taken from Howe 2003.[89]

There are many viewpoints on the issue of multiple primaries and the clinical significance is not always appreciated. This is particularly true of brain and CNS tumours, where tumours can be particularly difficult to classify based on histology, creating ambiguity in the definition of "separate entities". Further, the timing interval of two months is not always relevant from a clinical standpoint.[89] In the current study, we have been relatively conservative in our approach to defining multiple primary tumours as this field is still under development. We believe that it is a pertinent issue that will need to be addressed in the future, but the relative paucity of diagnostic information available to us from analysing only pathology records (sometimes including only biopsy results) has lead us to take a more conservative approach to diagnosing multiple primary tumours of the brain.

Rules[84, 89]

1. Differences in histological subtype are considered by United States Registries according to the first three digits of ICD/SNOMED code (see **Tables 1.7 and 1.8**). If multiple tumours occur at the same site, and the first three digits are the same, they are considered the same tumour, and one entry is completed. For example, choroid plexus carcinoma (M**939**0) and an ependymoma (M**939**1). If the first three digits are different, the tumours are considered different, and separate entries are completed. For example astrocytoma (M**940**0) and a gemistocytic astrocytoma (M**941**1). We have not used this definition in the current study and instead coded only the more specific diagnosis. Exceptions to this rule are if the multiple tumours are of a completely separate tissue of origin, for example, grade 4 malignant glioma + meningioma. Although this would tend to underestimate our incidence rate, we have been able to use this definition in the current study due to our low rate of non-specific codes. Additionally, it was thought that

a more conservative approach to incidence determination was more desirable than overestimation.

2. Laterality was used for multiple non-malignant tumours to determine if the tumours were two separate primary tumours but not malignant tumours.
3. If a non-malignant tumour of the same histology and at the same site demonstrated a recurrence, it was counted as the same tumour regardless of timeframe (e.g. 2 months, 2 years, 20 years). If the same situation is encountered for a malignant tumour, the current United States practice is to code this as a second primary and complete an additional entry. Again, we have opted not to follow this practice so as not to overestimate the incidence rate.
4. A tumour is considered of a different site based on the first three digits of the ICD-O codes outline above (**Table 1.7**). For example, multiple tumours occurring in "**C71**.0 Cerebrum" and "**C71**.2 Temporal Lobe" are the same tumour, and only one entry is completed. Multiple tumours occurring in "**C70**.0-**C70**.9 Meninges" and "**C71**.0 Cerebrum" are considered two different tumours, and two separate entries are completed.

1.9 Statistical Methods

A multicentre retrospective analysis of histologically confirmed primary benign and malignant brain tumours was conducted over the years 2000-2008. ~12,200 records from all 13 pathology departments servicing all 22 (23 if including the Mater Hospital) tertiary referral centres in the ACT/NSW region were collected. Non operative cases were collected from the region's largest stereotactic radiosurgery centre. Data were cleaned and analysed according to current international coding and statistical practice.

1.9.1 Hardware/Software

Descriptive information was tabulated and analysed for total numbers of tumours by age group, gender and histology using the following computer programs;

- Microsoft Excel 2007 version 12.0
- SPSS software version 17.0.
- Joinpoint Regression[90]

1.9.2 Standardisation

Age-specific rates are calculated by dividing the number of cases occurring in each specified age group by the corresponding population in the same age group expressed as a rate per 100,000 population. Rates are adjusted for age to aid comparisons between populations that differ in age structure. In the current study direct standardisation is used, in which the age-specific rates are multiplied against a constant population (the 2006 Census population, 2000 US standard population and WHO World standard 2000-2025 populations). Population data were obtained from the Australian Bureau of Statistics Census 2006 data.

1.9.3 Age Specific Groupings

All tumours were analysed in accordance with international literature for ease of comparison of rates in three major age groupings; 0-19 years, 20-64 years, and 65 years and above.[4]

1.9.4 Recurrence of Tumours

Recurrence of tumours was controlled for at the collection stage by data collectors as previously described. These tumours were removed from the final analysis, with only the earliest date of diagnosis being included.

1.9.5 Weighting of Data

Incidence rates were age standardised using the direct method and weighted against age, gender, year and postcode. An average weighting of 3.21%, calculated from both public and private Australian hospital separation data (2006-7),[91] was applied to the data to account for patient outflow from the study region. Inflows were controlled for by manual exclusion of postcode of residence. To account for completeness of data as well as migration effect an overall average weighting of 5.00% was used.

1.9.6 Analysis of Significance – Joinpoint Regression

Log-linear Poisson regression, in which the logarithmic incidence rate (dependent variable) was calculated as an exponential function over time (independent variable) and the data (assumed to have a Poisson distribution), was used to statistically compare trends over time[4, 92]. Trends were expressed as annual percentage change (APC) over the 9-year period, with corresponding two-

sided 95% confidence intervals (CI) using up to two joinpoints with log-linear modelling for average annual percentage change calculation (AAPC). Trends were also analysed in the same fashion over the period 2001-2006.

Joinpoint Regression software version 3.3.1 was obtained from the ACT Cancer Registry and used to identify any sharp changes in the incidence over the time period studied. Joinpoints correspond to the point in time of a change in trend where several different lines come to a juncture. The software fits the simplest joinpoint model that the data will allow using a series of permutation tests[4] using the Monte Carlo Permutation method for significance testing.[92]

1.10 References

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Chapter 2. A multicentre study of primary brain tumour incidence in Australia (2000-2008)

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Abstract

There are conflicting reports from Europe and North America regarding trends in the incidence of primary brain tumour, whereas the incidence of primary brain tumours in Australia is currently unknown. We aimed to determine the incidence in Australia with age-, sex-, and benign-versus-malignant histology-specific analyses. A multicenter study was performed in the state of New South Wales (NSW) and the Australian Capital Territory (ACT), which has a combined population of >7 million with >97% rate of population retention for medical care. We retrospectively mined pathology databases servicing neurosurgical centres in NSW and ACT for histologically confirmed primary brain tumours diagnosed from January 2000 through December 2008. Data were weighted for patient outflow and data completeness. Incidence rates were age standardised and trends analysed using joinpoint analysis. A weighted total of 7651 primary brain tumours were analysed. The overall US-standardised incidence of primary brain tumours was 11.3 cases 100 000 person-years (±0.13; 95% confidence interval, 9.8–12.3) during the study period with no significant linear increase. A significant increase in primary malignant brain tumours from 2000 to 2008 was observed; this appears to be largely due to an increase in malignant tumour incidence in the ≥65-year age group. This collection represents the most contemporary data on primary brain tumour incidence in Australia. Whether the observed increase in malignant primary brain tumours, particularly in persons aged ≥65 years, is due to improved detection, diagnosis, and care delivery or a true change in incidence remains undetermined. We recommend a direct, uniform, and centralized approach to monitoring primary brain tumour incidence that can be independent of multiple interstate cancer registries.

Keywords: Australia, brain tumour, incidence, primary neoplasm.

Introduction

In the 1970s and 1980s, an increased incidence of brain tumours was reported internationally and correlated with the emergence of imaging technologies, such as computed tomography (CT) and magnetic resonance imaging (MRI),[11, 16, 17] and wider clinical awareness of brain tumours.[2] In Australia, a small number of descriptive epidemiologic studies of primary central nervous system (CNS) tumours were published in series from Melbourne, Tasmania, and Adelaide[20-23] from the early 1990s. One Victorian study[20] of 4577 tumours reported age standardised incidence rates of malignant CNS tumours of 5.0 cases per 100 000 males and 3.4 cases per 100 000 females but reported no significant trends during the period 1986–1988 regarding specific histological subtypes. The other Victorian study[21] analysed 3575 cases of primary benign and malignant brain tumours over the period 1982–1990, with no clear trend in incidence. The Tasmanian study[22] analysed 1752 cases from 2 registries during the period 1978–1992 and reported increasing age-standardised primary brain cancer incidence rates in males (from 16.3 to 26.2 cases per 100 000 person-years) and females (from 9.7 to 18.0 cases per 100 000 person-years) aged ≥75 years, most prominently in cases of glioblastoma multiforme (GBM). The Adelaide study[23] was a short study of a low sample population, showing an increased risk of glioma among women who reported working with cathode-ray tubes. During the early 1990s, when use of CT and MRI technology became widespread in Australia, no change in national brain cancer incidence was observed by the Australian Institute of Health and Welfare (AIHW).[93] In fact, a decrease was observed, particularly for females. Despite changes in brain tumour pathology classification that occurred during the AIHW report canvassing period of 1982–2004,[94] again no significant trends were demonstrated in the AIHW data (**Figure 2.1**).

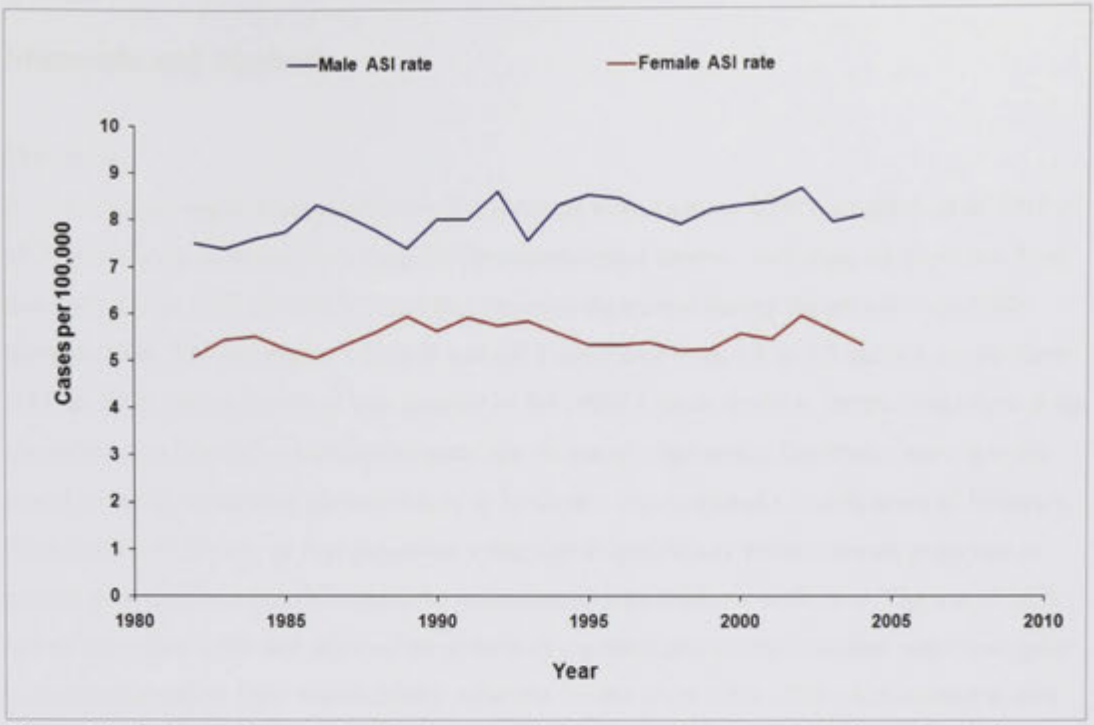

Figure 2.1. Incidence data calculated by the Australian Institute of Health and Welfare (AIHW) for "Malignant neoplasm of brain" (*International Classification of Diseases, 10th Revision*, C71) over the period 1982–2004.[93]
The incidence represented in the graph above is age standardised using 2001 Australian census data as the standard population. According to the AIHW graph, little change in the brain tumour incidence has been seen in Australia over 22 years, despite changes in reporting, classification, and population demographics during this time.

A number of reports regarding primary brain tumour incidence are derived from North American[4, 7-10, 17] and European[2, 16] sources. One of the most comprehensive is the 2007–2008 Statistical Report of the Central Brain Tumour Registry of the United States (CBTRUS)[10] which provides a primary CNS tumour age-adjusted incidence of 18.2 cases per 100 000 people in 2004. According to the 2002–2003 Statistical Report of CBTRUS,[7] the incidence was 13.4 cases per 100 000 people in 1995. Given that CBTRUS reports CNS tumour incidence age-adjusted to the 2000 US standard population and that the period of these reports is well embedded in the MRI era in the United States, the observed increase in incidence of ~36% in <1 decade is not likely to be adequately explained by an "aging population" or by "better diagnosis." However, the change may in part be due to variations in methodologies used by sources contributing to the CBTRUS database and to delayed tumour reporting or "late ascertainment"[15] from its 15–19 cooperating state registries. Given the limited data regarding the primary brain tumour incidence from Australasian sources, our goal was to determine the incidence in Australia with age-, sex-, and benign versus malignant histology-specific analyses and trends.

Materials and Methods

Database

A retrospective multicenter analysis was performed from January 2009 through August 2010 of all 13 pathology databases servicing the 24 neurosurgical centres, including all major teaching hospitals, in the ACT and NSW recording tumours diagnosed during the period from 2000 through 2008. The population of NSW and ACT increased from 6.8 to 7.3 million people from 2000 to 2008. Ethics approval was granted by the NSW Cancer Institute for the collection of de-identified data from all nominated centres (see Acknowledgements). Databases were queried based on the *Systematized Nomenclature of Medicine, International Classification of Diseases, 10th Edition* (ICD-10), or text diagnoses using either specifically written search programs or pre-existing database search engines by a nominated data collector at the site. The use of fully identifiable data at the site allowed for control of repeated presentations to that institution prior to de-identification. Data were initially collected for the years 1994–2008, with complete data from all centres available from mid-1999.

Inclusion and Exclusion Criteria

Approximately 12 000 records were analysed for the period of diagnosis (2000–2008), with exclusion of records based on diagnosis, topography, and completeness, yielding a total of 7251 records for final analysis. All tumours were microscopically confirmed. Systemic lymphoma and metastatic, extracerebral, and germ cell tumours (n = 1800) were excluded from the analysis. Tumours in patients from overseas or other Australian states and territories were also excluded from the analysis (n = 450). Discrepancies in data completeness were followed up with the collecting institution, and if further specific searches did not yield more complete data, the records were excluded from the analysis (n = 50). A large number of re-entrant and recurrence data were excluded (n = 2450), the majority (56%) of which came from the conglomeration of 4 databases at the 1 centre. The analysis included pituitary, craniopharyngeal duct, and pineal tumours; haemangioma; hemangiopericytoma; primary central nervous system lymphoma; and cranial nerve tumours (Supplemental Appendix 1).

Coding and Grading

ICD-10 and SNOMED classification systems were used to code all records at the central site by a limited number of professional coders to maximize consistency of coding. Reporting and coding rules were followed according to the 2004 guidelines of the Centres for Disease Control and Prevention,[95] with the important exception that pilocytic astrocytoma was coded as a benign rather than a malignant tumour. Tumours were graded according to the 2007 World Health Organization (WHO) Classification of Tumours publication[82] and assigned topography

according to the Surveillance, Epidemiology, and End Results (SEER) program coding advice.[96] The initial—but not any re-presenting—diagnosis of each patient was used for our analysis. If 2 separate entries for the same patient differed in tumour grade, the higher grade of tumour was used, provided that the entries occurred within 8 weeks of each other. If the time difference in entries was greater than this period, the initial diagnosis and grade were used.

Population Selection and Standardisation

The ACT and NSW populations were used to benefit from the relatively low outward migration rate. Cross-border flows were estimated using 2008 Australian Hospital Statistics data for public and private hospitals[91] and an overall weighting for patient outflow, inflow, and data completeness of 5% was used. Population data were obtained from the Australian Bureau of Statistics Census 2006. Incidence rates were age adjusted using the direct method and were standardised to the 2001 Australian Standard and 2006 Australian Census population in 5-year age groupings. Incidence rates were also standardised to the 2000 US Standard Population and 2000 World Standard Population using the direct method of analysis. Unless otherwise specified, reporting of incidence rates has been limited to US-standardised rates for ease of comparison with existing literature.

Statistical Analysis

Descriptive information was tabulated for total numbers of tumours by age group, sex, and histology in both Microsoft Excel, version 2007, and SPSS software, version 17.0. Log-linear Poisson regression in which the logarithmic incidence rate (dependent variable) was calculated as an exponential function over time (independent variable) and in which the data were assumed to have a Poisson distribution was used to statistically compare trends over time.[4, 97] Trends were expressed as annual percentage change (APC) over the 9-year period, with corresponding 2-sided 95% confidence intervals (CIs) using up to 2 joinpoints with log-linear modelling for average annual percentage change calculation (AAPC). Joinpoint Regression software, version 3.3.1, was obtained from the ACT Cancer Registry and was used to identify any sharp changes in the incidence during the time period studied. Joinpoints correspond to the point in time of a change in trend in which several different lines come to a juncture. The software fits the simplest joinpoint model that the data will allow using a series of permutation tests[4] using the Monte Carlo Permutation method for significance testing.[97] Incidence rates are expressed as mean ± standard deviation.

Results

Description of the Data

The final weighted data set included 7651 primary brain tumours, with a total of 698–935 tumours per year from 2000–2008. Persons aged 0–19 years represented ~6% of all tumours, whereas the majority (63%) of tumours were represented in persons aged 20–64 years, with the remaining 30% represented by persons ≥65 years. Relatively equal proportions of tumours were represented among male and female patients (49% and 51%, respectively). Fifty-eight percent of tumours were benign (WHO grade I or II), whereas 42% were malignant (WHO grade III or IV), with minimal (cumulative 3.1%) representation in the data of nonspecific codes (**Table 2.1**). Elderly adults (age, ≥65 years) recorded the largest proportion of malignant tumours (52%), whereas children (age, 0–19 years) and adults (age, 20–65 years) demonstrated a preponderance of benign tumours, with only 34% and 38% being malignant, respectively (**Figure 2.2a**)).

Morphology	Frequency, no.	Percentage
Astrocytoma high-grade, NOS	74	1.0
Astrocytoma low-grade, NOS	82	1.1
Glioma high-grade, NOS	62	0.8
Glioma low-grade, NOS	11	0.2

Table 2.1. Frequency and percentage of total of nonspecific (NOS) codes

Incidence Trends

This study found an overall US-standardised incidence rate for primary brain tumours of 11.3 cases per 100 000 person-years (±0.13; 95% CI, 9.8–12.3 cases per 100 000 person-years during the study period, with no significant linear increase observed (**Figure 2.2b**)). An overall crude rate of 11.8 cases per 100 000 person-years (range, 10.1–12.7 cases per 100 000 person-years) was calculated for the study period. Rates were slightly higher among males but more variable in females (11.7 ± 0.26 cases per 100 000 person-years [95% CI, 10.0– 12.6 cases per 100 000 person-years] and 11.4 ± 0.25 cases per 100 000 person-years [95% CI, 10.0–13.0 cases per 100 000 person-years, respectively), but again with no obvious linear increase and well below latest reported US rates (**Figure 2.2c**)). No significant trends were demonstrated for benign tumours when analysed by sex and age groupings. Of note, an overall significant increase in primary malignant brain tumours was observed over the study period from 2000 to 2008 (APC, 3.9; 95%CI, 2.4– 5.4) (**Figure 2.3a**)), particularly since 2004 (overall AAPC, 3.9; 95% CI, 2.6–5.2). Of note, data since 2004 have not yet been published by the AIHW, and only preliminary data from the NSW Cancer Registry are available (see below). This overall increasing trend in malignant tumours was consistent for both males (APC, 2.3; 95% CI, 0.4–4.2) and females (APC, 2.3; 95% CI, 0.3– 4.3)—again, particularly since 2004 (AAPC for males, 2.3 [95% CI,

0.7–3.9]; AAPC for females, 2.3 [95% CI, 0.6–4.0]) (**Figure 2.3b**)). Driving this increase is the increase in malignant tumours in the ≥65-year age group (APC, 1.54; 95% CI, 0.1–3.0) (**Figure 2.3c**)), with no significant difference by sex (**Table 2.2**).

Subgroup	No. of cases	APC	(95% CI)
All persons			
Brain tumours	7651	1.2	20.6 to 3.0
Benign tumours	4445	1.7	21.4 to 4.9
Malignant tumours	3206	3.9[b]	2.4 to 5.4
Malignant tumours			
Males	1907	2.3[b]	0.4 to 4.2
Females	1299	2.3[b]	0.3 to 4.3
Persons aged ≥65 years			
Malignant tumours	1223	1.54[b]	0.1 to 3.0
Men	693	2.6	22.7 to 8.2
Women	530	0.6	22.1 to 3.4

Table 2.2. Overall incidence rate trends, by annual percentage change (APC), for primary brain tumours from the Australian Capital Territory and New South Wales populations[a]
CI indicates confidence intervals.
[a]All models use exponential Poisson regression and were adjusted for age group.
[b]Denotes significance of the APC. Note that APC values are statistically significant from the value 0.

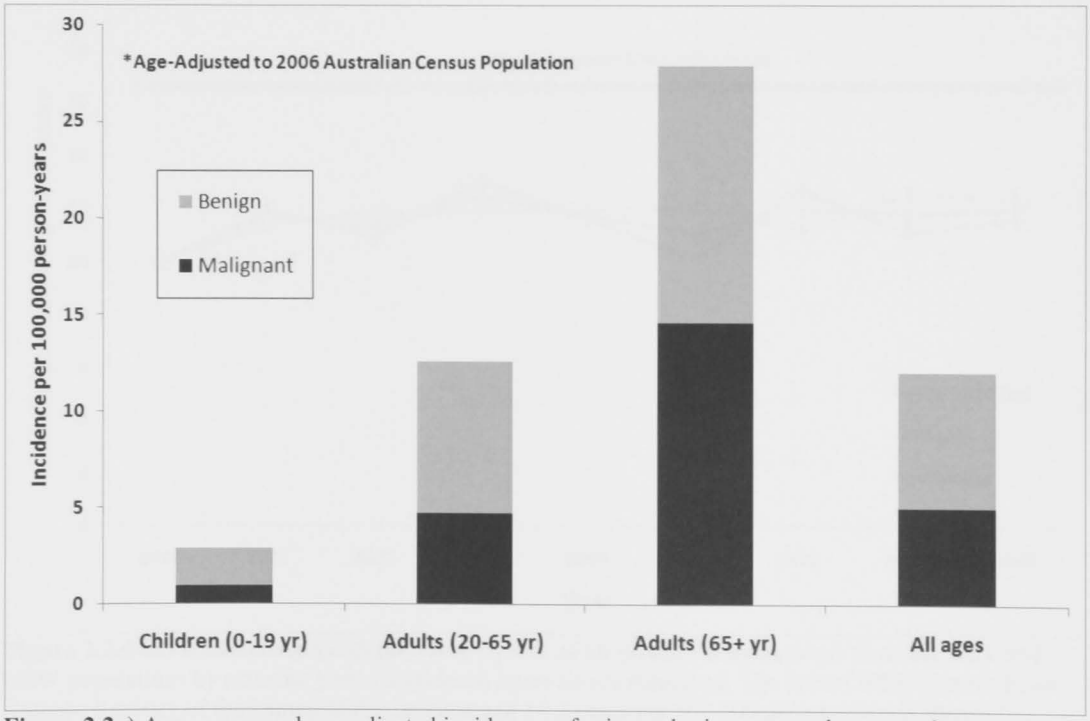

Figure 2.2a) Average annual age-adjusted incidences of primary brain tumours, by age and proportionally by behaviour. Data have been age-adjusted to 2006 Australian Census data. Benign, World Health Organization (WHO) grade I and II tumours; malignant, WHO grade III and IV.

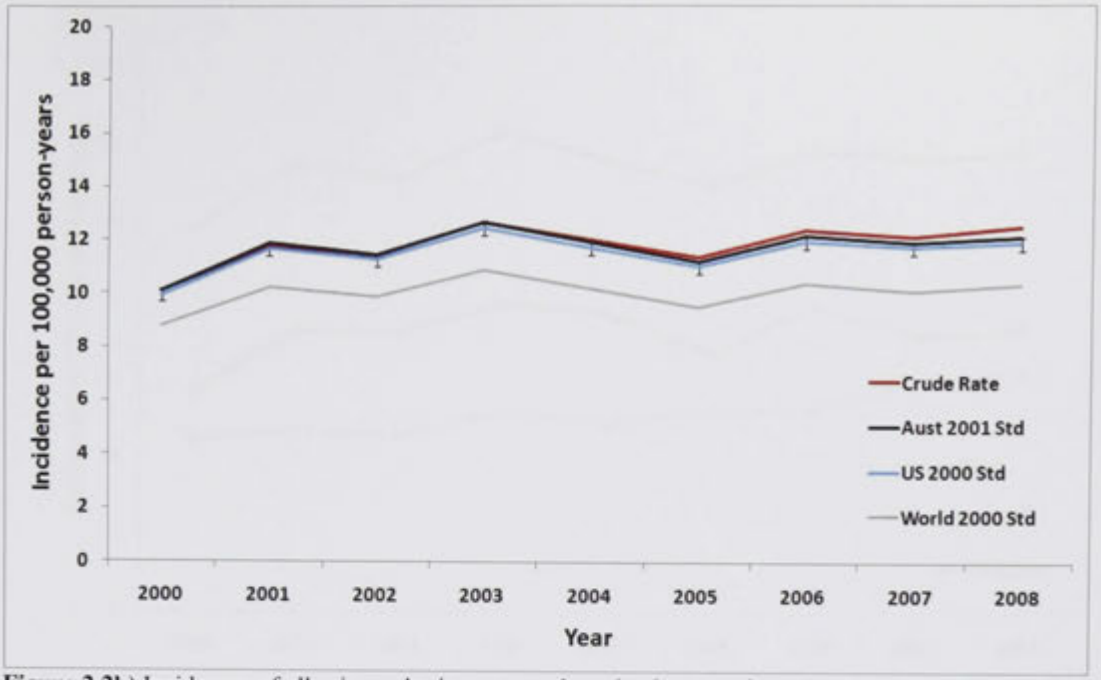

Figure 2.2b) Incidences of all primary brain tumours, by calendar year, from the Australian Capital Territory (ACT) and New South Wales (NSW) populations. Rates are age standardised to the 2001 Australian Standard, the 2000 US standard, and 2000 World standard populations. To avoid congestion, confidence intervals are displayed for the US-standardised trend only.

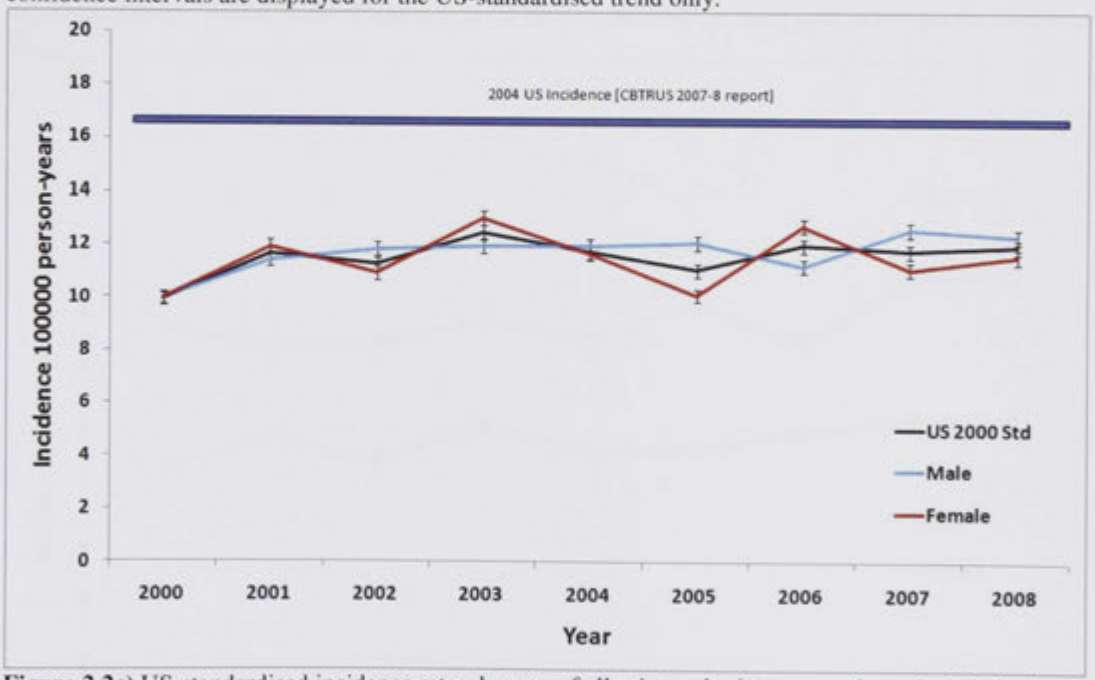

Figure 2.2c) US-standardised incidence rates, by sex, of all primary brain tumours from the ACT and NSW populations by calendar year. Confidence intervals are displayed. The latest (2008) Central Brain Tumour Registry of the United States incidence of 18.2 cases per 100 000 person-years is shown.[10]

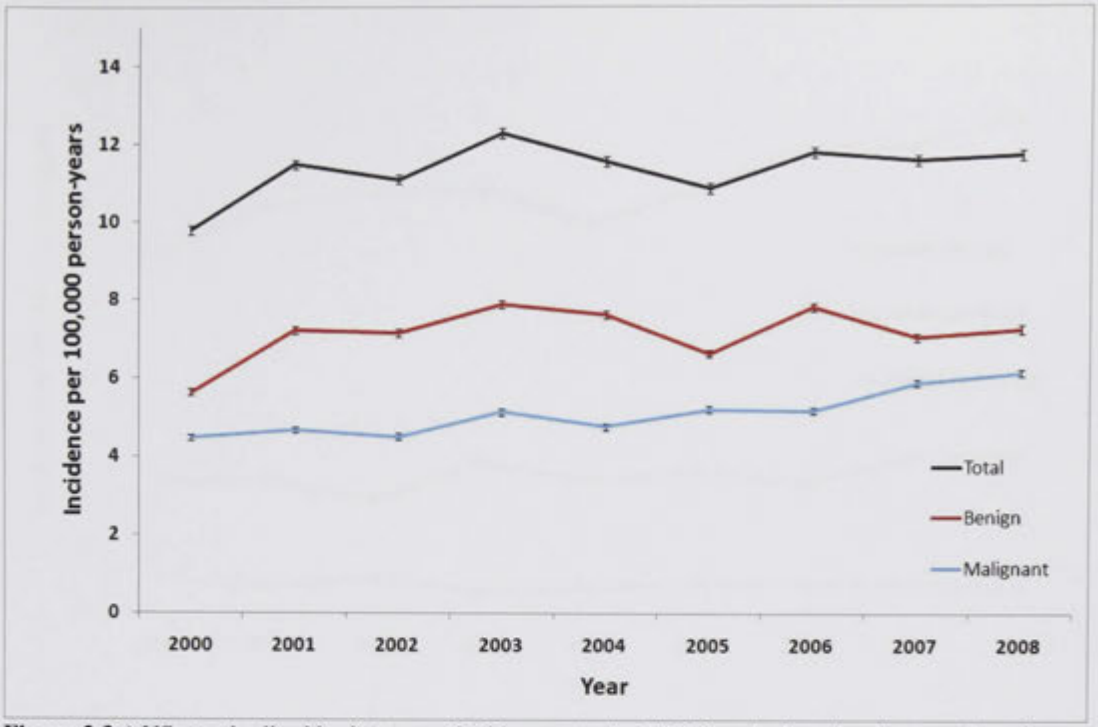

Figure 2.3a) US-standardised brain tumour incidence rates by WHO grade, by calendar year, from the Australian Capital Territory (ACT) and New South Wales (NSW) populations. Confidence intervals are displayed. Benign, World Health Organization (WHO) grades I and II; malignant, WHO grades III and IV.

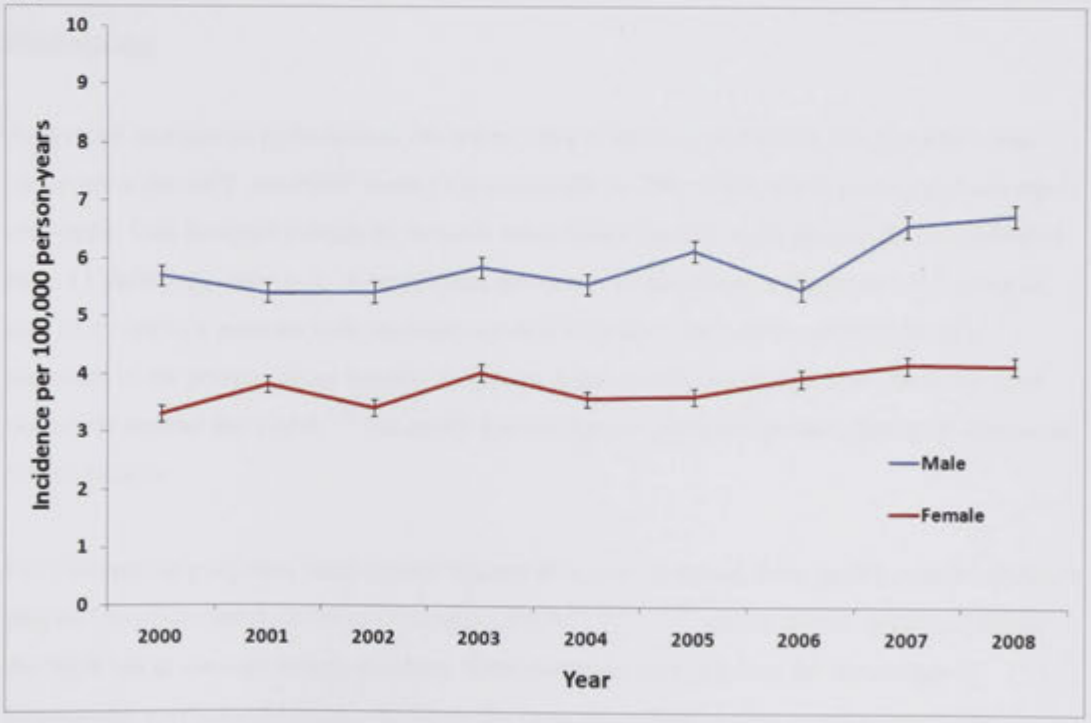

Figure 2.3b) US-standardised malignant brain tumour incidence rates, by sex and calendar year, from the ACT and NSW populations.

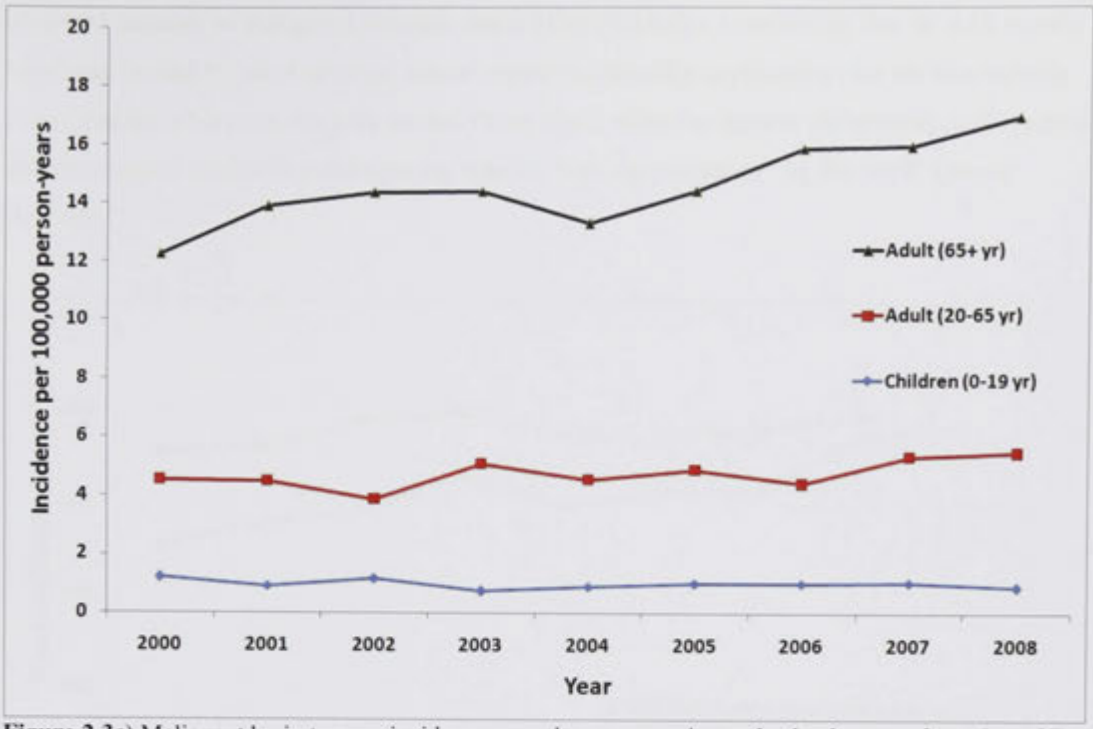

Figure 2.3c) Malignant brain tumour incidence rates, by age grouping and calendar year, from the ACT and NSW populations.

Discussion

An overall increase in age-adjusted incidence rates of primary malignant brain tumours was observed in the ACT and NSW during the period 2000–2008, particularly among persons aged ≥65 years. One hundred percent of tumours were histologically confirmed, with data collected from 13 pathology units (i.e., directly from the source of histological diagnosis), servicing an area of >7-million persons with minimal outward migration for health services. Similar increases in the primary brain tumour incidence in the elderly population have been reported elsewhere around the world,[3, 16] but to our knowledge, no comparable study has been conducted in Australasia.

For comparison purposes, local cancer registry data were obtained from yearly cancer incidence reports from November, 2006 to December, 2009,[28, 62, 64, 98-100] with numbers prior to 2004 for the ACT being average annual numbers. Case numbers were adjusted for percentage of histological verification (mean, ~85%) on the basis of published rates to aid comparison. Overall raw numbers from the current study are less than the combined ACT and NSW Cancer Registry numbers, particularly in the earlier years of the study period (**Figure 2.4**)). The difference in raw numbers between the 2 sets may reflect a different definition of "malignant" brain tumours. More notable, however, is an upward trend in raw tumour numbers seen in both data sets, but most marked in our study, particularly in the latest years of 2007 and 2008. This

observed increase in malignant tumours noted by us is curious, considering that no such reports have been issued by the Australian cancer registries. Possible explanations for the discrepancy in raw numbers between our data set and those of the registries include differences in diagnostic and histological definitions and data lag time or "late ascertainment" by the NSW Cancer Registry.[15]

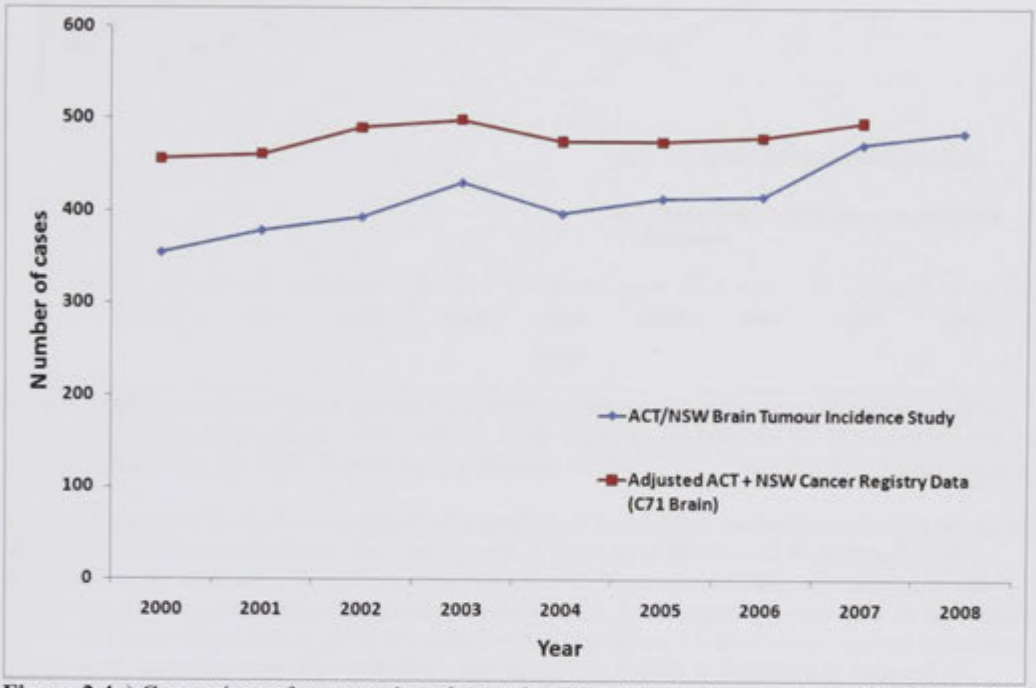

Figure 2.4a) Comparison of case numbers for **total** malignant brain tumours, Australian Capital Territory (ACT) and New South Wales (NSW), 2000–2008, by sex between the current study and the combined data from the NSW Central Cancer Registry (CCR)[28, 62, 64, 100] and the ACT Cancer Registry.[10, 16, 98, 99]

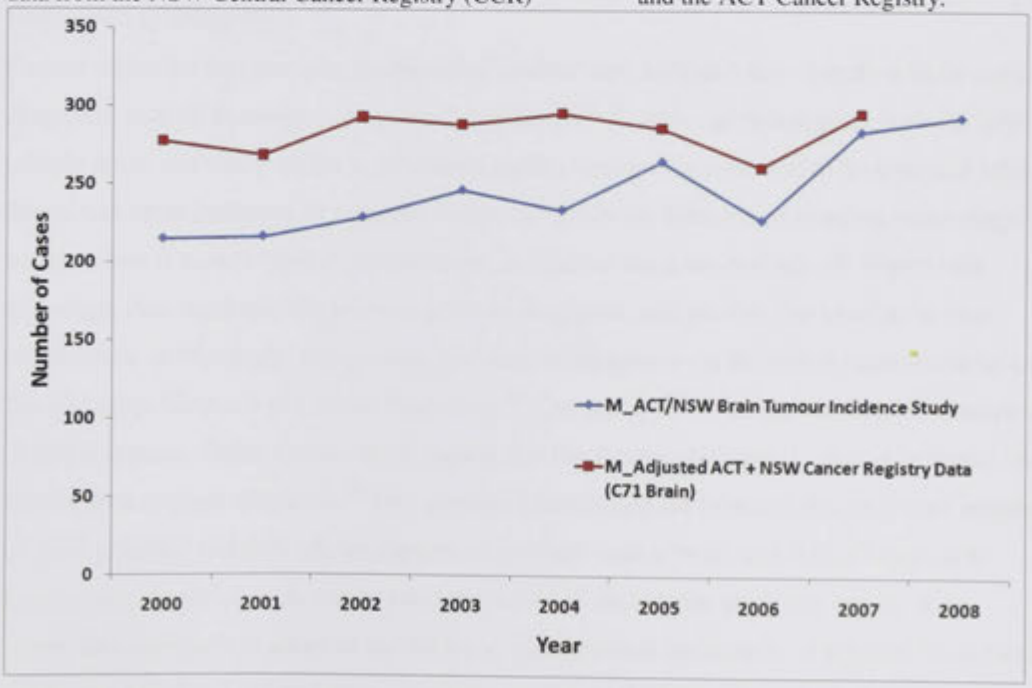

Figure 2.4b) Comparison of case numbers for male malignant brain tumours, Australian Capital Territory (ACT) and New South Wales (NSW), 2000–2008, by sex between the current study and the combined data from the NSW Central Cancer Registry (CCR)[28, 62, 64, 100] and the ACT Cancer Registry.[10, 16, 98, 99]

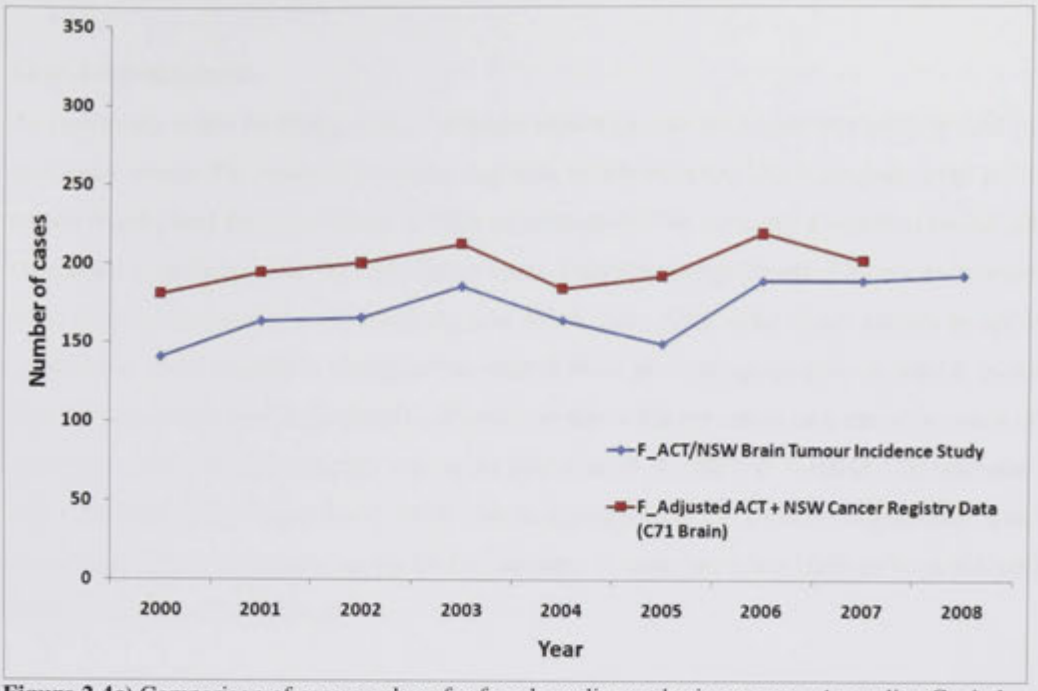

Figure 2.4c) Comparison of case numbers for female malignant brain tumours, Australian Capital Territory (ACT) and New South Wales (NSW), 2000–2008, by sex between the current study and the combined data from the NSW Central Cancer Registry (CCR)[28, 62, 64, 100] and the ACT Cancer Registry.[10, 16, 98, 99]

Case numbers have been adjusted according to published histological verification rates per year and by sex (mean, ~85%) to aid comparison. The Australian Institute of Health and Welfare mentioned previously is the Australian Government body monitoring brain tumour data collection across the whole nation, whereas the aforementioned sources are state based. For comparison purposes, we have included all World Health Organization grade II tumours with/3 (malignant) behaviour per current collection practices of Australian registries, despite the ambiguity this creates in definition of tumours as benign/non-malignant.

Definition of Diagnosis

Cancer registries and previous independent studies have included non-operative brain tumour diagnoses as well as tumours diagnosed at autopsy.[10, 16] Although this approach yields large sample sizes, our study aimed to provide a greater acuity in assessment of histological subtypes that is lost upon inclusion of tumours diagnosed solely on the basis of imaging technology, conservative (i.e., non-operative) treatment, or clinical decision-making. Of importance, pathology data represent the primary point of diagnosis, and provide the most up to date information on histology, topography, and time of diagnosis—a definition more consistent with the European Network of Cancer Registries.[101] Our study involved the histological confirmation of every tumour. Other sources have argued that the timing of diagnosis should be based on the date of first *clinical* diagnosis.[10] This approach is justified for tumours that are either inoperable or slow growing and thus allows capture of tumours with a "wait-and-watch" approach. Logistically, however, this was beyond the scope of the current study but would be an interesting approach to adopt in the future as an additional component of primary brain tumour incidence. Our local Australian cancer registries quote 85% histological confirmation, and a 15% addition in tumour numbers would no doubt enhance the current study.

Late Ascertainment

As previously noted by Clegg et al.,[15] delayed reporting may lead to downwardly biased incidence trends. The study of 9 cancer registries involved in the SEER program over a 17-year period highlighted the importance of "late ascertainment" by comparing reported initial (after a standard 2-year delay) and final incidence rates. They found significant differences between these rates and estimated a reporting lag time of ≥4 years. This delay likely applies to our own Australian cancer registries, owing to the sheer bulk of processing required to publish incidence rates from multiple different sources. We believe that we have minimized the occurrence of this bias in our study by referring directly to the data sources themselves—namely, all relevant pathology units assessing primary brain tumour specimens in the chosen geographical area. Our results may thus be reconciled with increasing rates in later years that have perhaps not yet been captured by registry methods.

Unknown Individual Subtype Trends

Finally, we suggest suboptimal coverage and reporting of specific histological subtypes by current surveillance methods. Unlike the United States, there is no mandatory collection of benign brain tumour data in Australia, although we have attempted to collect both benign and malignant primary brain tumour data in a timely fashion. We have been unable to access the raw data of our local registries, but their public reports quote malignant brain tumour rates in terms of *International Classification of Diseases, Oncology 3*, C71 topography and morphology classifications. A number of reports discuss tumours not necessarily considered to be malignant brain tumours, such as low-grade astrocytoma, oligodendroglioma, and ependymoma.[28, 62, 64, 100] Furthermore, the latest report from the NSW Cancer Registry included melanoma, germ cell, embryonal, and soft-tissue tumours in its analysis.[62] This creates ambiguity in the comparison of rates. Finally, an unknown proportion of "unspecified" tumours are used for determination of the incidence by the cancer registries. Although this is an unavoidable consequence of their collection methods, it is a limitation we have endeavoured to minimize through direct collection of histological diagnoses (100% in our study's database versus an average of 85% in our local cancer registry databases), as evidenced by a ~3% rate of non-specific histological diagnoses in our study (**Table 2.1**).

Limitations

The main limitations of the current study are the unavailability of identifiable data throughout the entire analysis and uncertainties regarding complete case capture rates. Control for re-presentations of 1 patient to multiple different institutions was difficult in the current study because of the use of multiple separate databases with limited cross-communication. Ethics approval for data matching of identifiable data was sought but not granted due to staff

shortages. We attempted to minimize this error, however, by controlling for repeated presentations to the one institution. Retrospective database mining inherently introduces an element of uncertainty in data quality that was compounded in the current study by the use of multiple different database systems and search methods. Issues around adequate coding of diagnoses, database technology, and diligence of data collectors contribute to this issue. The use of dedicated data collectors employed by the local pathology units and multiple site visits helped minimize this uncertainty. In view of the limitations presented, we need to be cautious in our approach to interpretation of the observed increase in primary malignant brain tumours. Additional examination of histological subtypes is currently being performed and the authors do not suggest an association with reported risk factors in the literature. However, because the observed increase in incidence is confined to malignant tumours among persons aged ≥65 years, we question whether an association between greater diagnostic capability/delivery of care[94] and tumour incidence is at play in the years 2000–2008 in Australia.

Australia is ~1 decade behind the United States and Europe in terms of the implementation of certain imaging technologies, with the introduction of CT and MRI imaging occurring in the late 1980s to mid-1990s in the ACT and NSW. Some authors suggest that the latest reported increases in incidence from the United States and Europe are not adequately explained by advances in imaging technology or a lower clinical threshold for scanning. We believe that monitoring of these trends in Australia over the next 10–15 years presents an ideal opportunity to discover potential associated risk factors in brain tumour development through the establishment of a central nationwide brain tumour registry that examines both benign and malignant tumours in a timely fashion. Exclusion of benign tumours produces a tendency to underestimate incidence and an undervaluing of the importance of benign brain tumours, some of which can progress histologically to cancer. This raises issues of feasibility and whether such a collection should be combined with existing brain tumour registries or established as separate entity, similar to the recent experience of the Austrian Brain Tumour Registry.[54]

Conclusion

To our knowledge, this collection constitutes the most contemporary data on primary brain tumour incidence in the Australasian region. Data were 100% histologically confirmed and were mined directly at the coal-face of brain tumour diagnosis from a relatively large and overall medically self-contained Australian subpopulation, minimizing the effect of late ascertainment of data and providing greater diagnostic specificity. It is unclear at this time whether the observed increase in malignant primary brain tumours, particularly among persons aged ≥65 years, is due to improved detection, diagnosis, and delivery of care or to a true change in

incidence. Australian Cancer Registry data have an average lag time of 4 years from collection to reporting, an experience shared by CBTRUS.[7-10] Given the current importance of identifying risk factors for specific brain tumours,[73] which we recognize is beyond the scope of a cancer registry, we believe that at an international level, our study supports consideration of the establishment of a centralized registry for each nation that (1) directly receives histologically confirmed primary brain tumour data from all relevant pathology units, and (2) analyses and reports data according to an international agreement regarding the precise definition of primary benign versus malignant histological subtypes suitable for collection.

Supplementary Material

Supplementary material containing an appendix to this paper is available online at Neuro-Oncology (http://neuro-oncology.oxfordjournals.org/).

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Conflict of interest statement. None declared.

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Chapter 3. Increasing incidence of glioblastoma multiforme and meningioma, and decreasing incidence of Schwannoma (2000-2008): Findings of a multicenter Australian study.

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Abbreviations:

ACT - Australian Capital Territory

APC - Annual percentage change

CBTRUS - Central Brain Tumour Registry of the United States

CI - Confidence interval

CNS - Central Nervous System

CT - Computed tomography

GBM - Glioblastoma multiforme

ICD-10 - International Classification of Diseases, 10th Edition

NSW - New South Wales

MRI - Magnetic resonance imaging

US - United States

SNOMED - Systematized Nomenclature of Medicine

SEER - Surveillance, Epidemiology and End Results Program

SRS - Stereotactic radiosurgery

WHO - World Health Organization

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Abstract

Background: The incidence of primary brain tumours is currently unknown in Australia. We report the second part of a retrospective multicenter study in the state of New South Wales (NSW) and the Australian Capital Territory (ACT), a combined population of >7 million with >97% retention rate for medical care.

Methods: Data from histologically-confirmed primary brain tumours diagnosed from January 2000 through December 2008 were weighted for patient outflow and data completeness, age-standardised and analysed using joinpoint analysis.

Results: A significant increasing incidence in glioblastoma multiforme (GBM) was observed in the study period (annual percentage change, 2.5; 95% confidence interval, 0.4-4.6, n=2275), particularly after 2006. In GBM patients in the ≥65-year group, significantly increasing incidence for men and women combined (APC, 3.0; 95% CI, 0.5-5.6) and men only (APC, 2.9; 95% CI, 0.1-5.8) were seen. Rising trends in incidence were also seen in meningioma for total male population (APC, 5.3; 95% CI, 2.6-8.1, n=515) and males aged 20-64 years (APC, 6.3; 95% CI, 3.8-8.8). Significantly decreasing incidence trends were observed for Schwannoma for the total study population (APC, -3.5; 95% CI, -7.2 - -0.2, n=492), significant in women (APC, -5.3; 95% CI, -9.9 - -0.5) but not men.

Conclusion: This collection is the most contemporary data on primary brain tumour incidence in Australia. Our registries may observe an increase in malignant tumours in the next few years that they are not detecting now due to late ascertainment. We recommend a direct, uniform and centralized approach to monitoring primary brain tumour incidence, including the introduction of non-malignant data collection.

Key Words: Australia, brain tumour, cancer, incidence, late ascertainment, primary neoplasm

Introduction

Trends in the overall incidence of primary brain tumours have been widely reported as either increasing,[2, 4, 16, 75] stable,[102, 103] or decreasing.[102] A large Danish study[2] of 11,935 cases of adult glioma between 1943 and 1997 reported a 1.7-fold increase in incidence from 2.2 to 3.7 cases per 100,000 person-years. Histological confirmation was found in almost all glioma cases in the last 20 years of that study. The authors also examined 4845 cases of adult meningioma during the same period and reported a 3.9-fold increase from 0.61 to 2.42 cases per 100,000 person-years. Surprisingly, the increasing incidence trend over time associated with glioma was seen to plateau after 1968, well before Denmark's introduction to computerized tomography (CT) in 1978 and magnetic resonance imaging (MRI) in 1985. On the other hand, the authors found that the incidence of meningioma continued to rise throughout the years studied, possibly related to a lower clinical threshold for imaging older patients. A second study of 18,630 cases of adult primary intracranial meningioma encompassed Denmark, Finland, Norway and Sweden from 1968 through 1997.[52] Increasing trends were again noted in both males (1.4 to 1.9 cases per 100,000 person-years) and females (2.6 to 4.5 cases per 100,000 person-years). The authors suggested this was due to widespread use of new imaging technologies.[52] The updated study however, covering the same region from 1974 to 2003 and almost 60,000 patients aged 20-79 years, showed increasing incidence rates for glioma and meningioma overall, but flattening of trends in the latest years 1998-2003.[51]

In the United States, Inskip et al.[102] analysed almost 40,000 brain cancer cases over a 30 year period from 1977 to 2006 using the SEER database and reported stable, even decreasing, overall incidence rates in most age groups. During the earlier study period 1977-1991, large and statistically significant increases were demonstrated in persons <30 years of age and ≥65 years of age. In the later study period (1991-2006), stable incidence was reported across the board, with the exception of females aged 20-29 years who showed a significant increasing trend in frontal lobe malignancies (APC, 4.27; CI, 1.88-6.71). Interestingly, although incorporating brain *cancer* (i.e. including metastatic disease but excluding meningioma and lymphoma) and thus not directly comparable to the current study, the authors highlight expected delay-adjustment with upward revision of incidence rates, so the observed increases may in fact be underestimates. This phenomenon termed "late ascertainment"[15] is common to many cancer registries and is associated with a data lag of 3-5 years that is also reflected in Australian registries.

An absence of any overall trends in the incidence of brain cancers in both males and females in the population of England in the period 1998-2007 was recently reported.[104] This stable

incidence trend, along with the levelling off of incidence trends in four Nordic countries during 1974–2003 has led some authors to conclude that mobile phones result in no significant increased risk of brain tumours.[51] However, the European study[51] was criticized for stopping case ascertainment in 2003,[58] and for not presenting results stratified by anatomic site.[105] In this regard, our recently published Australian study[106] reported a significant increase in malignant tumour incidence most evident from 2006 onwards. Further, the English study that reported no change in overall incidence did report results stratified by anatomic site and found significantly increased rates of tumours of the temporal lobe in both men and women, and increased rates in frontal lobe tumours in men only. Such changes may not be due to chance occurrence.[107] Regardless of risk association,[43, 58, 73] these data reflect an ongoing need for incidence trend monitoring of both malignant and non-malignant tumours.

Given the limited data regarding primary brain tumour incidence from Australasian sources, our goal was to develop an understanding of the Australian incidence with age-, sex-, and pathology-specific analyses and trends. Further, because Australia lags behind the US and Europe by several years in terms of imaging technology and mobile phone use, we feel that now is an optimal time to begin data collection and pave the way for future association studies.

Materials and Methods

A full account of our methods has been published recently.[106]

Database

A retrospective multicenter analysis was performed from January 2009 through July 2010 of all 13 pathology databases servicing the 24 neurosurgical centres, including all major teaching hospitals, in the ACT and NSW recording brain tumours diagnosed during the period from 2000-2008. The population of NSW and ACT increased from 6.8 to 7.3 million people between 2000 and 2008. Databases were queried with control for repeated presentations and tumoural recurrence to individual institutions. Data was initially collected for the years 1994-2008, with complete data from all centres available from mid-1999.[106]

Inclusion and exclusion criteria

Approximately 12,000 records were analysed for the period of diagnosis (2000-2008), with exclusion of records based on diagnosis, topography, and completeness, yielding a total of 7251 records for final analysis. All tumours were microscopically confirmed at a single pathology department but no independent review was performed as this was beyond the scope of the current study. Systemic lymphoma, metastatic, extracerebral and germ cell tumours were

excluded from the analysis (not presented but discussed in our previous paper), as were tumours in patients from overseas or other Australian states and territories. The analysis included pituitary, craniopharyngeal duct and pineal tumours, haemangioma, hemangiopericytoma, primary central nervous system (CNS) lymphoma, and cranial nerve tumours.[106]

Coding and grading

ICD-10 and SNOMED classification systems were used to code all records according 2004 guidelines of the Centres for Disease Control and Prevention.[95] Tumours were graded according to the 2007 World Health Organization (WHO) Classification of Tumours publication.[82] The initial but not any re-presenting diagnosis of each patient was used for our analysis.[106]

Standardisation and statistical analysis

The ACT and NSW populations were used to benefit from the relatively low outward migration rate. Cross-border flows were estimated at 3.2% using 2008 Australian Hospital Statistics data for public and private hospitals[91] and an overall weighting for patient outflow, inflow, and data completeness of 5% was used. Incidence rates were age-adjusted using the direct method and were standardised to the 2001 Australian Standard and 2006 Australian Census population in 5-year age groupings. Incidence rates were also standardised to the 2000 US Standard Population and 2000 World Standard Population using the direct method of analysis. Unless otherwise specified, reporting of incidence rates has been limited to US-standardised rates for ease of comparison with existing literature. Log-linear Poisson regression was used to statistically compare trends over time.[4, 97, 106] Trends were expressed as annual percentage change (APC) over the 9-year period, with corresponding 2-sided 95% confidence intervals (CI) using up to 2 joinpoints with log-linear modelling for average annual percentage change calculation (AAPC). Trends were also analysed in the same fashion over the period 2001-2006. Joinpoint Regression software version 3.3.1 was used to identify any sharp changes in incidence as described elsewhere.[106]

Results

Incidence by pathology

The most frequently encountered histology was a malignant tumour, glioblastoma multiforme (GBM; 30%, n=2275) followed by a predominantly non-malignant tumour, meningioma (24%, n=1865). Pituitary tumours and Schwannoma accounted for 13% (n=960) and 6% (n=492) of all tumours, respectively. Primary malignant tumour incidence was found to have increased by approximately 35% between 2000-2008 (APC, 3.9; 95% CI, 2.4-5.4) with most of this increase occurring after 2006 (**Figures 3.1a), 3.1b), 3.1c**)).[106]

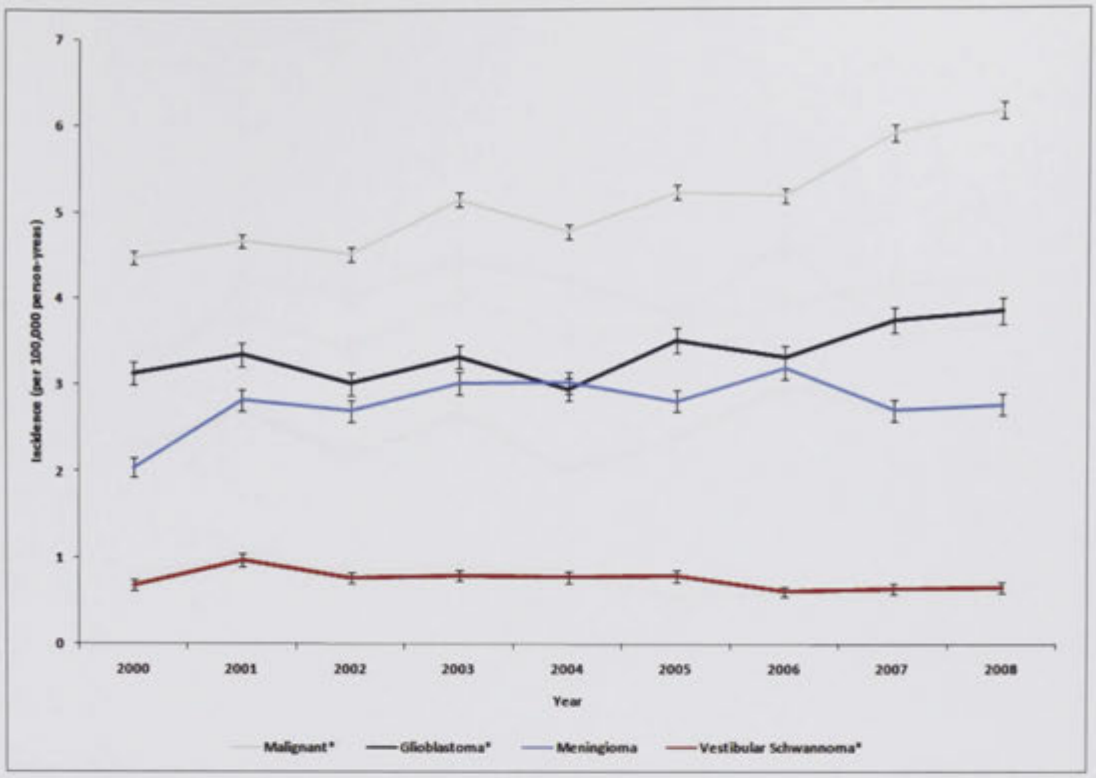

Figure 3.1a) US-standardised brain tumour incidence rates for total population by major histological groupings by calendar year from the Australian Capital Territory (ACT) and New South Wales(NSW) populations.

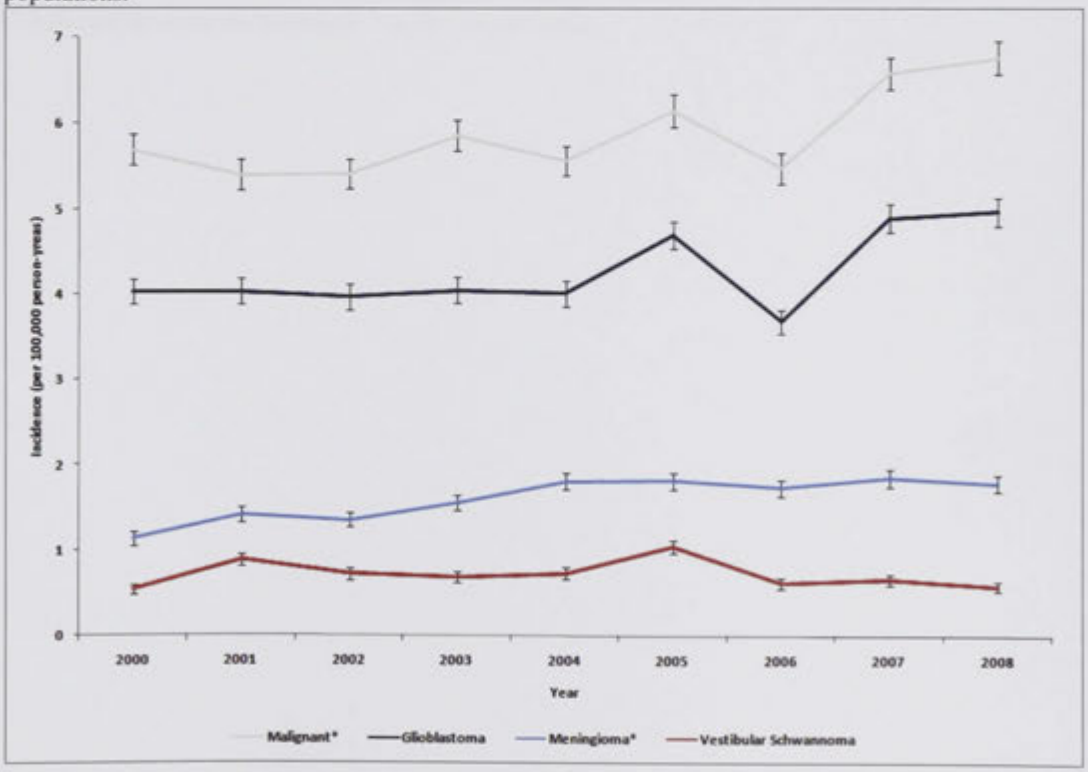

Figure 3.1b) US-standardised brain tumour incidence rates for male population by major histological groupings by calendar year from the Australian Capital Territory (ACT) and New South Wales(NSW) populations.

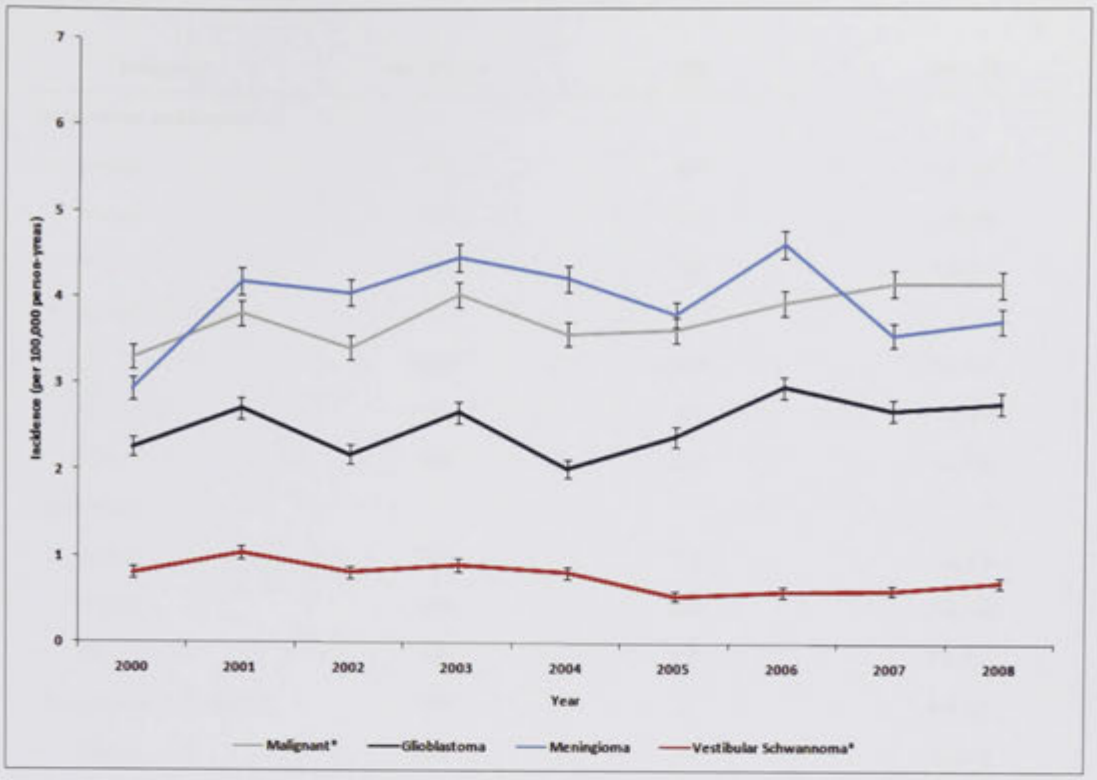

Figure 3.1c) US-standardised brain tumour incidence rates for female population by major histological groupings by calendar year from the Australian Capital Territory (ACT) and New South Wales(NSW) populations.
Confidence intervals are displayed. * denotes significance.

Subgroup	No. of cases	APC	(95% CI)
Glioblastoma multiforme			
All persons	2275	2.5*	0.4, 4.6
Women	885	2.2	-1.5, 6.0
Men	1390	2.6	-0.1, 5.4
Persons aged ≥65 years			
All	1027	3.0*	0.5, 5.6
Women	438	3.2	-2.9, 9.6
Men	589	2.9*	0.1, 5.8
Meningioma			
All persons	1865	1.9	-1.6, 5.5
Women	1350	0.6	-3.6, 5.0
Men	515	5.3*	2.6, 8.1
Persons aged 20 to 64years	1227	1.9	-0.9, 4.9
Women	936	0.5	-3.2, 4.4
Men	291	6.3*	3.8, 8.8
Schwannoma			
All persons	491	-3.5*	-7.2, -0.2
Women	258	-5.3*	-9.9, -0.5
Men	233	-1.0	-7.9, 6.3

Table 3.1: Overall incidence rate trends, by annual percentage change (APC), for primary brain tumours from the Australian Capital Territory and New South Wales populations**.
CI indicates confidence intervals.
**All models use exponential Poisson regression and were adjusted for age group.
* Denotes significance of the APC. Note that APC values are statistically significant from the value 0.

Glioblastoma

A weighted total of 2275 GBM (n=2197, 96.5%), gliosarcoma (n=62, 2.7%) and giant cell glioblastoma (n=17, 0.7%) were collected during the years 2000-2008, with a 1.6:1 male:female predominance. A significant increase in incidence of all GBM from 3.22 to 3.96 cases per 100,000 person-years was observed in the study period of 2000-2008 (APC, 2.5; 95% CI, 0.4-4.6) (**Figure 3.1a**)). During the same period, in patients in the ≥65-year group, the incidence rates increased from 10.30 to 14.42 cases per 100,000 person-years (APC, 3.0; 95% CI, 0.5-5.6) for both men and women combined (**Figure 3.2**). This significant increase held for men (13.55 to 18.71 cases per 100,000 person-years; APC, 2.9; 95% CI, 0.1-5.8) but not for women (7.77 to 10.92 cases per 100,000 person-years; APC, 3.2; 95% CI, -2.9 – 9.6) (**Table 3.1**; **Figure 3.2**).

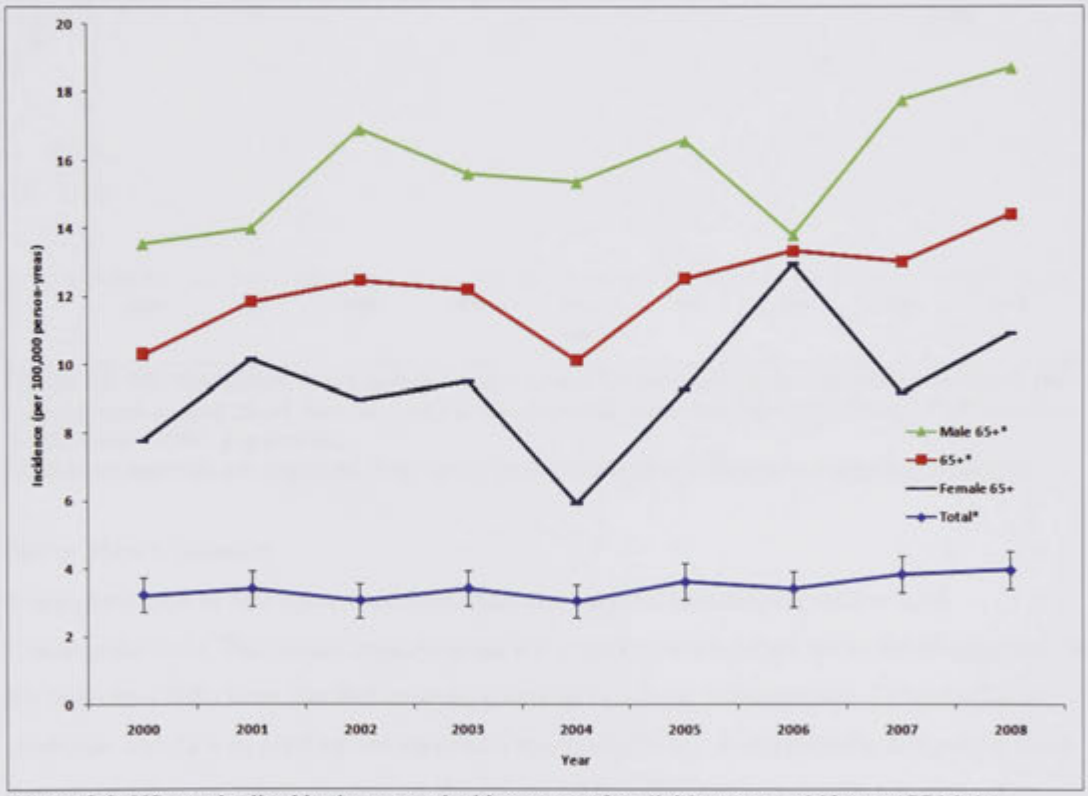

Figure 3.2: US-standardised brain tumour incidence rates for glioblastoma multiforme (GBM) by calendar year from the Australian Capital Territory (ACT) and New South Wales (NSW) populations for total population, total population aged 65 and above, and male population aged 65 and above. Confidence intervals are displayed. All three trends show significant (*) increase using joinpoint analysis.

Meningioma

A weighted total of 1865 meningiomas were collected during the period 2000-2008, with a 2.6:1 female:male predominance. Of these tumours, 92% were WHO Grade I, 7% WHO II, and 1% WHO III. From 2000-2008 a significantly increasing incidence trend in meningioma in men, both for total male population (APC, 5.3; 95% CI, 2.6-8.1, n=515) and in males aged 20-64 years (APC, 6.3; 95% CI, 3.8-8.8) was observed (**Table 3.1**; **Figures 3.1b) & 3.3**). Incidence

rates ranged from 1.1 to 1.8 cases per 100,000 person-years in the period 2000-2008 for all meningioma, and 1.2 to 2.0 cases per 100,000 person-years for men aged 20 to 64.

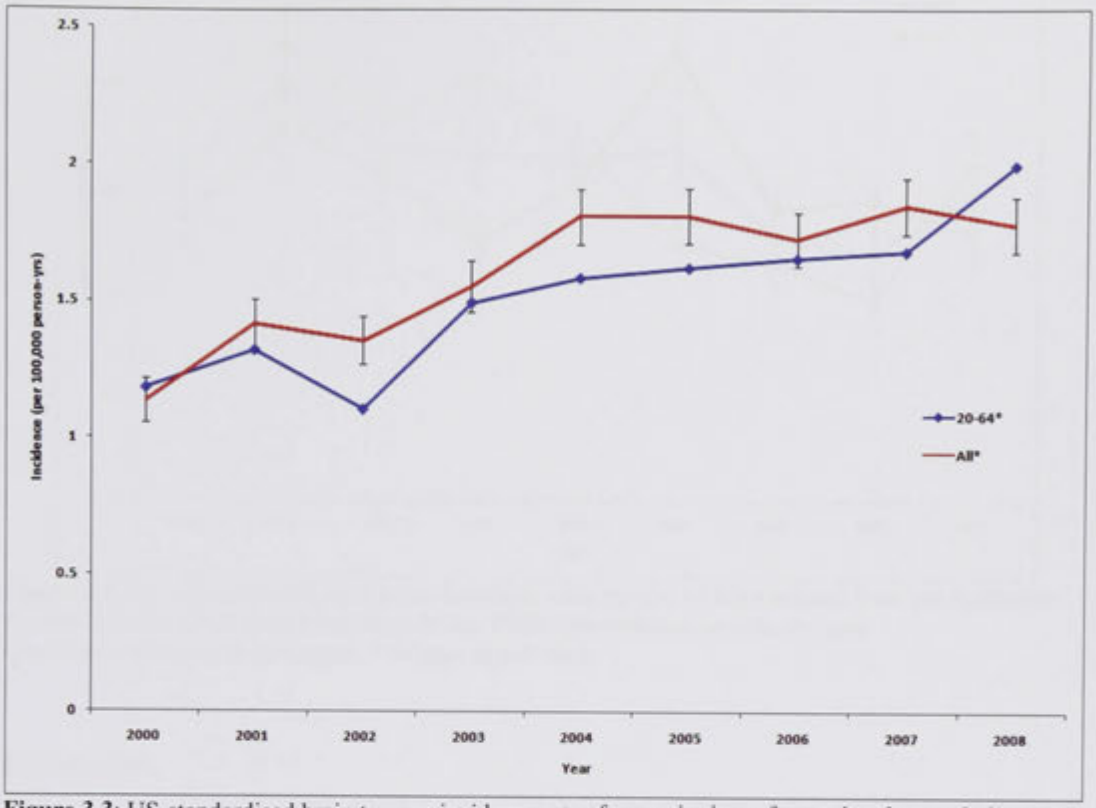

Figure 3.3: US-standardised brain tumour incidence rates for meningioma for total male population, and male population aged 20-64 years by calendar year from the Australian Capital Territory (ACT) and New South Wales (NSW) populations.
Confidence intervals are displayed. Both trends show significant (*) increase using joinpoint analysis.

Nerve sheath tumours

A weighted total of 492 nerve sheath tumours were used in the analysis, with a 1.1:1 female:male ratio. The current collection did not include extra-cerebral nerve sheath tumours, so the majority (76%) were labelled acoustic neuroma/vestibular Schwannoma, 12% labelled as cerebellar and 12% as cerebral not-otherwise specified (NOS). A significantly decreasing trend was observed in all Schwannomas for the period 2000-2008 (APC, -3.5; 95% CI, -7.2- -0.2), that was significantly present in women (APC, -5.3; 95% CI, -9.9 - -0.5) but not in men (APC, -1.0; 95% CI, -7.9 – 6.3) (**Table 3.1**; **Figures 3.1a), b), c) & 3.4**). Part of our dataset on non-malignant tumours included collection of non-histologically-confirmed data from the largest stereotactic radiosurgery (SRS) centre in the region. Even upon exclusion of the SRS data, analysis for both meningioma and nerve sheath tumours in the period 2000-2008 maintained the significant trends described above (data not shown).

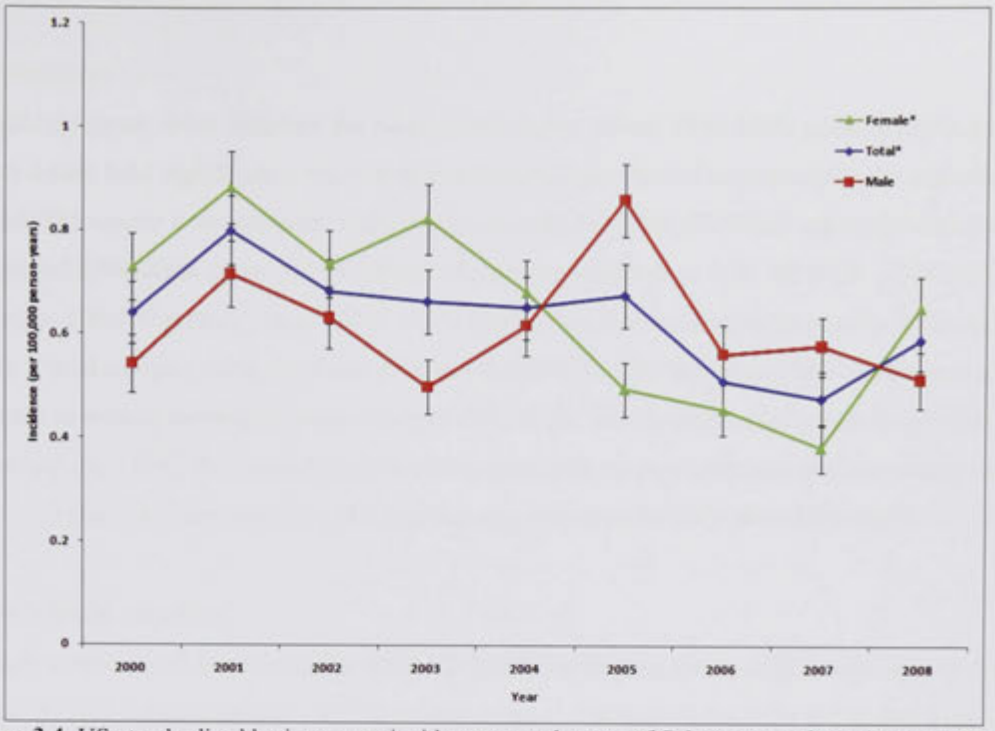

Figure 3.4: US-standardised brain tumour incidence rates, by sex, of Schwannoma from the Australian Capital Territory (ACT) and New South Wales (NSW) populations, by calendar year. Confidence intervals are displayed. * denotes significance.

Discussion

The key finding of this two-part study[106] is a significant increase in primary malignant brain tumours, particularly GBM, occurring over the time period 2000-2008, especially evident after 2006.

Glioblastoma

The recent published incidence rates (2004-2006) from the Central Brain Tumour Registry of the United States (CBTRUS) for GBM (3.17 ±0.04 cases per 100,000 person-years)[10] are similar to rates from the present study averaged over the period (~3.4 ± 0.51 cases per 100,000 person-years). Incidence rates and trends over the period 2000-2008 from our study are also similar to the Danish results discussed above.[2] Further, when our data were analysed using multiple joinpoints in the time period 2001-2006, that is, the years for which there are corresponding published Australian cancer registry data, no significant increase was seen (data not presented). Our findings are therefore also consistent with the most up-to-date data on malignant tumours from our local cancer registries, except that the increasing trend we report herein is largely due to the higher brain cancer incidence observed in the years 2007 and 2008, data that may not have as yet been received and/or analysed by Australian registries. Our relatively early access to these data via the direct analysis of local pathology databases has been discussed in the first part of this study.[106]

Meningioma

Significant trends were observed for meningioma in the period 2000-2008, particularly in men. These trends held significance when non-histologically-confirmed tumours from the region's largest SRS centre were excluded (data not presented).The 2010 CBTRUS report for data from the period 2004-2006 quotes the incidence of male meningioma as 3.76 (95% CI, 3.70-3.83) cases per 100,000 person-years.[10] This rate is higher than US standardised rates from the present study. Trend analysis using the same database (CBTRUS) over the years 1985-1999 reported an increase in overall meningioma incidence (AAPC, 1.5),[4] but no significant trends by gender. Incidence rates from the current study are thus more akin to observed rates and increasing trends for meningioma in Europe during the approximate period 1970-2000 described above.

Nerve sheath tumours

Female nerve-sheath tumours in the 2010 CBTRUS publication quote an incidence rate of 1.60 (95% CI, 1.57-1.64) cases per 100,000 person-years.[10] Although these rates are higher than US standardised rates for vestibular Schwannoma in the present study, CBTRUS data also include both malignant and non-malignant nerve sheath tumours in the quoted rate. A study examining vestibular Schwannoma data from two sources (CBTRUS 1995-1999, and the Los Angeles County Cancer Surveillance Program 1995-1998) found average annual incidence rates of 0.55 (95% CI, 0.51-0.58) and 0.80 (95% CI, 0.66-0.94) cases per 100,000 person-years respectively in females.[46] Incidence for nerve-sheath tumours was approximately 1.07 cases per 100,000 person-years for both sources in the same study. These rates are more in keeping with the present study.

A recent study from Denmark presenting 2283 cases of vestibular Schwannoma over a 42-year study period reported increasing incidence from 0.31 to 2.28 tumours per 100,000 person-years between 1976 and 2004, and stabilizing at 1.94 tumours per 100,000 person-years in 2008.[108] The study is unique in that all cases of vestibular Schwannoma in Denmark are referred to a single centre for treatment, and the data have been prospectively entered into a database since 1976. Increased clinical awareness and technological advances in MR imaging technology seem to have accounted for the increase in incidence and the 2008 rate is considered by those authors as a true incidence. Australia is only 5-10 years behind Denmark in terms of imaging technology, with the first MR scanner in Denmark being introduced in 1985. Our rates of vestibular Schwannoma are considerably less than those reported in Denmark, and show a decreasing trend. This may be due in part to changing clinical practice in the treatment of vestibular Schwannoma towards non-operative (SRS) management.

Strengths and limitations of this study

We are primarily concerned with histologically-confirmed primary intracerebral tumours and our collection excludes tumours diagnosed solely based on clinical, imaging and post-mortem examination. Our study has a relatively high rate of histological specificity, with a low rate of non-specific codes used,[106] and we believe this strength will allow more precise and timely trend analysis through sourcing of brain tumour incidence data at the point of definitive diagnosis, namely, the pathology department. We also consider it a methodological strength that a different definition of "malignant" tumours has been used in the present study when compared to established Australian practice. Our definition is based on WHO Grade III and IV tumours and excludes lymphoma, metastatic disease, germ cell and extracerebral tumours, whereas Australian registries include WHO Grade II tumours of uncertain/borderline behaviour amongst others in their definition.[28, 62, 64, 100, 106] Defining brain tumours in terms of the WHO Classification of CNS tumours allows the use of the most contemporary and widely used classification system in the international literature, and thus a more optimal comparison of rates within and between countries.

The limitations of our study have been described in our preceding publication.[106] Briefly, the main limitations we encountered involved uncertainty regarding completeness of case capture rates due to lack of standardisation, lack of independent pathological review of diagnoses, lack of multiple sources of notification, the presence of cross-talk between databases and lack of control for re-entry of data from the one patient visiting multiple different institutions in the study area (an uncommon situation anecdotally). Although we have attempted to validate our incidence rates through direct comparison of malignant rates with our gold standard in Australia (i.e. the Cancer Registries), we acknowledge that there is no such comparator for non-malignant tumours in Australia. This implies a cautious approach when interpreting our published non-malignant tumour rates but at the same time provides the first Australian insight into their "ball-park" incidence rates.

Conclusion

The current study represents the most contemporary collection of primary brain tumours in Australia and underpins the importance of continued monitoring. We observed significant increases in incidence rates for GBM, particularly after 2006, and meningioma at rates comparable to recent US and European data. Incidence trends for Schwannoma, in contrast to the European experience, were observed to be significantly decreasing, but were akin to reported rates from the US. We recommend a direct, uniform and centralized approach to monitoring primary brain tumour incidence, as well as the introduction of non-malignant data collection.

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Chapter 4. Discussion

The current study represents the best estimate of brain tumour data in Australia, including both benign and malignant rates for all primary intra-cranial tumours.

Chapter 3 describes the overall incidence trends for the period 2000-2008 analysed by age, gender and WHO grade (published March 2011). A significant increase in primary malignant brain tumours was observed; that appeared to be largely accounted for by the increase in malignant tumours in the 65+ age group.

Chapter 4 presents subtype analysis of incidence data for the same period (2000-2008) with comparison to ACT/NSW Cancer Registry malignant tumour data (accepted for publication). Our results follow a very similar trend to the ACT/NSW Cancer Registry published trends for malignant tumours in the period 2001-2006, suggesting a **sound collection methodology** in this period. Data from 2007 and 2008 is not yet available from the Cancer Registries.

An important trend resulting from the benign data collection in the present study was an increasing trend in the years 2000 - 2008 and 2001-2006 for meningioma, particularly for males. A significant decrease in the incidence of vestibular Schwannoma was observed in the same period. This is data for which we have no direct comparison in Australia.

A number of procedures and quality checks were used to maximise data quality in the collection. Indicators suggest there was some bias around migration. Consequently, a weight was used to make adjustments using Australian Institute of Health and Welfare migration flows.

The trends presented from the collection here establish a good estimate of rates of brain tumours for Australia. The process has also established a considered methodology for launching a more formal and routine collection. Registries may see an increase in malignant tumours in the next few years that they are not seeing now due to late ascertainment.

4.1 Incidence Rates, Trends and Comparison to Australian and International Data

From the results, we observe no linear increase or decrease in overall incidence trends for all primary brain tumours. US-standardised incidence rates varied from 9.95 to 12.47 cases per 100,000 person years in the period 2000-2008. **Table 4.1** below shows a comparison of US standardised incidence rates from the current study and sequential reports from the CBTRUS database. Incidence rates in the current study are below those reported by CBTRUS.

Diagnosis Year	**CBTRUS Report**					**Current Study**
	2002-2003	**2004-2005**	**2005-2006**	**2007-2008**	**2010**	
1995	13.4					
1996	14					
1997	14.2	13.5				
1998	14.5	13.9	14.2			
1999	14	14.1	14.5			
2000		14.2	14.8	15.2		**9.95**
2001		14.7	15.3	15.9		**11.66**
2002			15.2	16.2		**11.28**
2003				17		**12.47**
2004				18.2		**11.75**
2005						**11.06**
2006					18.71	**11.99**
2007						**11.78**
2008						**11.94**

Table 4.1. Age-adjusted incidence of primary CNS tumours in the sequential reports of CBTRUS. Adapted from Khurana et al.[43] Rates are expressed in cases per 100,000 person-years.

The most common type of Tumours of Neuroepithelial Tissue included glioblastoma (~57%, n = 2276), astrocytoma (~20%, n = 820) and oligodendroglioma (10%, n = 404) (**Figure 4.1**). Glioblastoma included all glioblastoma, gliosarcoma and giant cell glioblastoma. Oligodendroglioma included both classic and anaplastic variants.

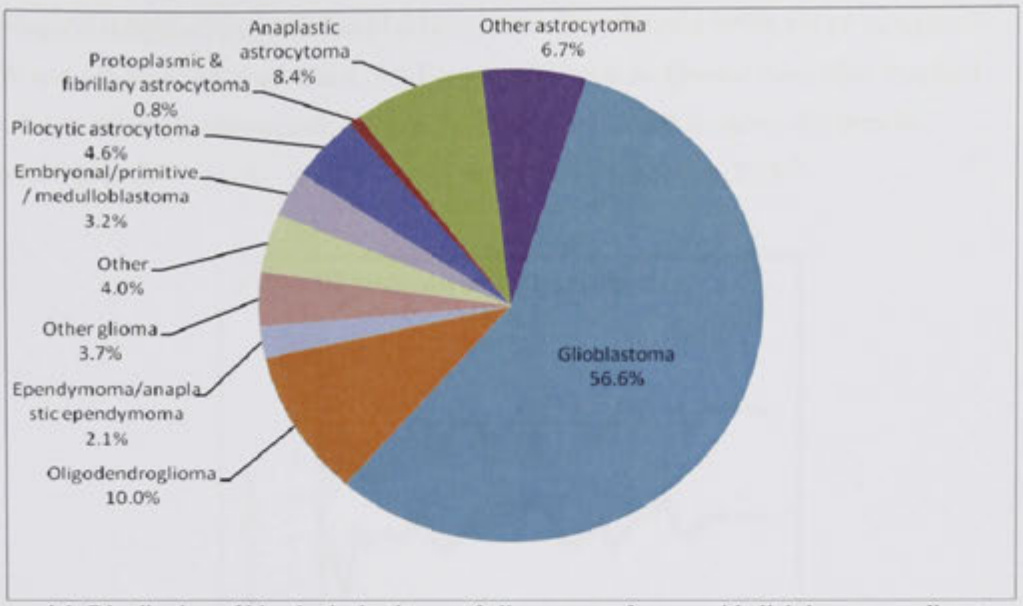


Figure 4.1. Distribution of histological subtype of all tumours of neuroepithelial tissue according to WHO Classification. Percentages are shown.

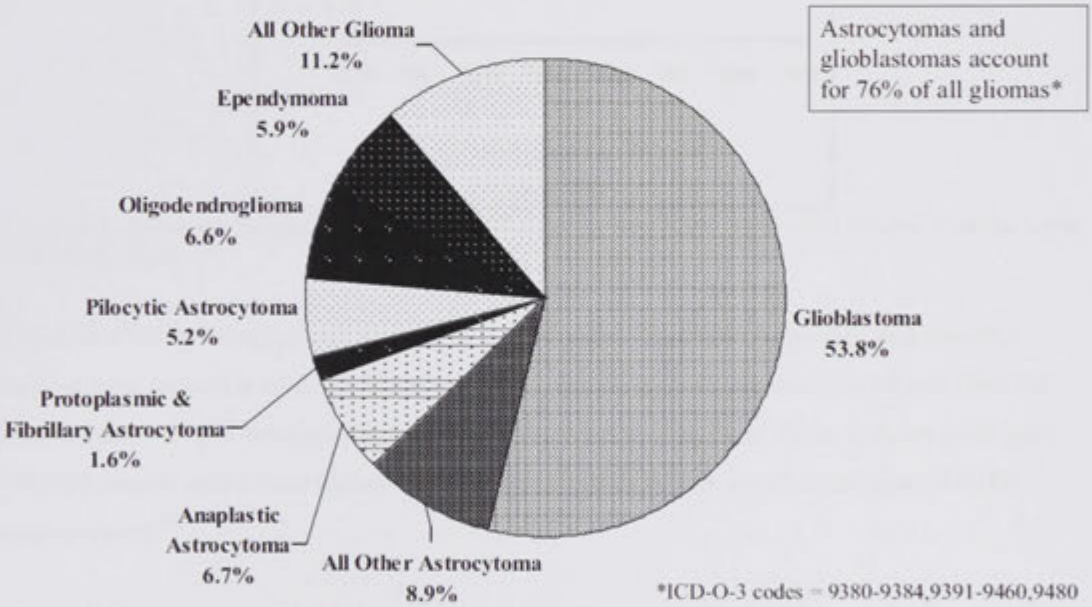


Figure 4.2. Distribution of All Primary Brain and CNS Gliomas by Histology Subtypes (n = 50, 240). CBTRUS Statistical Report: NPCR and SEER Data from 2004 – 2006.[10]

Comparing **Figure 4.1** to **Figure 4.2** above, the spread of tumours seen in the current study are very similar to the latest published CBTRUS rates.[10] This adds weight to the quality of collected data and gives us an objective comparator to validate our published results while also suggesting that overall Australian incidence rates follow similar trends to US rates. This is further supported by review of **Tables 4.2 and 4.3** below.

The latest publication from the NSW Central Cancer Registry described collection of astrocytic tumours (n = 363), oligodendroglial tumours (n = 40) and gliomas of uncertain origin (n = 37)

in 2007. The least frequent tumour collected was ependymal tumours (n=8). Incidence rates for histological subtypes have remained fairly constant since the mid-1990s for all subtypes in NSW and are expected to remain at 2007 levels (**Figure 4.3**). Quoted Australian standard population adjusted rates include 8.0 and 5.4 cases per 100,000 in males and females respectively in 2007 and 8.1 and 5.4 cases per 100,000 expected in 2021.[62]

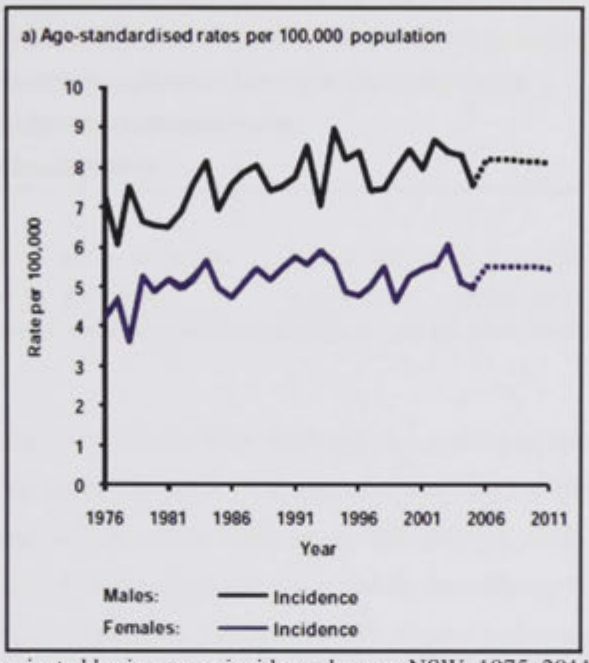


Figure 4.3. Actual and projected brain cancer incidence by sex, NSW, 1975–2011. Taken from the latest NSW CCR report.[62]

Figure 4.4 below compares NSW CCR data with other Australian Registries and selected international registries with similar reporting standards. Age-standardised incidence rates for brain cancer in NSW between 1998 and 2002 were 6.6 in males and 4.6 in females cases per 100,000 person-years, with highest rates being recorded in Victoria (7.2 cases per 100,000 person-years).[62]

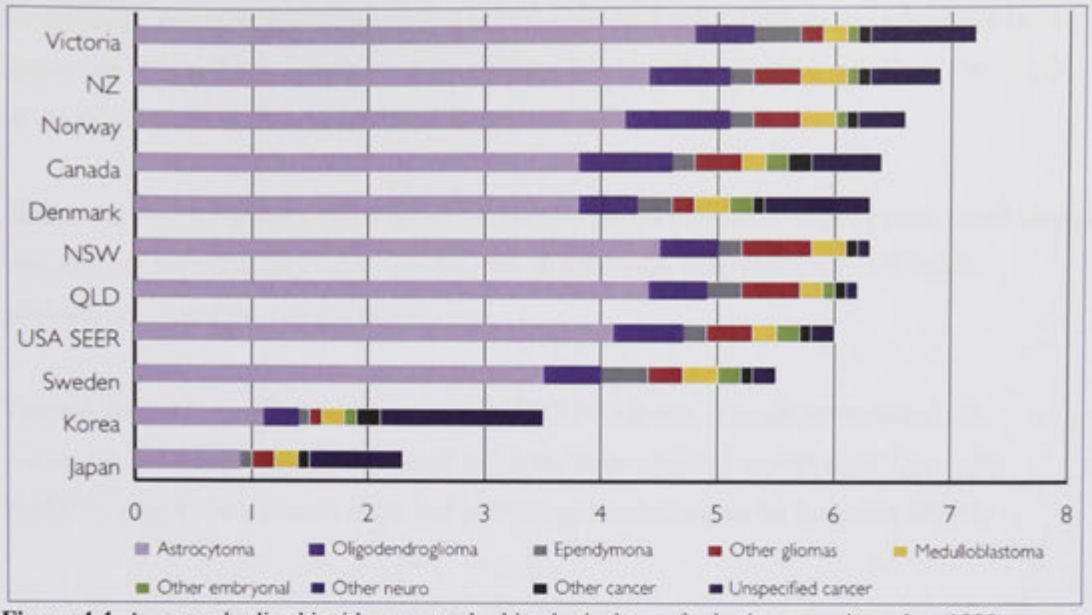


Figure 4.4. Age-standardised incidence rates by histological type for brain cancer in males (1998-2002).[62]

The main point of divergence from the NSW CCR practice and comparison of rates is in histological subtype definition. The NSW CCR and databases listed in **Figure 4.4** publish incidence rates by *behaviour* rather than *WHO grade*. This practice yields higher numbers but tumours that are considered "non-malignant" are included, thus diluting the meaning of the rates. For example, astrocytic tumours (comprising 75% of total brain cancers in the NSW collection) are a heterogenous population of tumour, with the majority (54%) being accounted for by glioblastoma (see **Figure 4.2**). Approximately 7% are anaplastic astrocytoma (WHO grade III) but the rest are WHO grade I and II tumours. That is, non-malignant tumours.

As mentioned, the focus on WHO grade vs. tumour behaviour is the point of divergence. A number of WHO grade II tumours if left untreated, have malignant potential, hence the focus on these tumours. This practice has arisen from changes in brain tumour classification over time and is explored in more detail below **Section 4.3.4 Change Over Time in Classification.**

Another example of this is ependymal and oligodendroglial tumours (approximately 6 and 7% of all tumours respectively, **Figure 4.2**). These tumours are again divided into WHO grade II and III but most of these types of tumours carry a malignant behaviour code.

Our practice follows the practice of the larger international databases (i.e. CBTRUS and Nordic studies) for ease of comparison with published rates.

Furthermore, our own neurosurgical and pathological background allows us to delineate more aggressive lesions from those that obtain curative therapy with complete resection. This is true of the WHO grade II lesions described above.

Tables 4.2 and 4.3 present major histological subtype (glioblastoma, meningioma, nerve sheath and pituitary tumours) incidence rates by year of collection from successive CBTRUS publications[7-10] and the current study.

Table 4.2 below, compiled from sequential CBTRUS reports, is again presented to aid discussion and comparison of published incidence rates with the current study. The latest CBTRUS report was released at the end of 2010 and includes data for the years 2004-6.

	Tumour	CBTRUS Report 2002-2003 1995-1999 data	2004-2005 1997-2001 data	2005-2006 1998-2002 data	2007-2008 2000-4 data	2010 2004-6 data
Total	Glioblastoma	3.24	3.01	3.05	3.09	3.17
	Meningioma	3.86	4.18	4.52	5.35	6.29
	Nerve Sheath	1.05	1.11	1.17	1.46	1.61
	Pituitary	0.92	0.82	0.92	1.37	2.40
	Total	**14.02**	**14.10**	**14.80**	**16.52**	**18.71**
Male	Glioblastoma	4.02	3.75	3.86	3.94	3.97
	Meningioma	2.46	2.57	2.75	3.17	3.76
	Nerve Sheath	1.07	1.12	1.19	1.48	1.63
	Pituitary	1.00	0.85	0.94	1.37	2.31
	Total	**14.22**	**13.92**	**14.50**	**15.77**	**17.44**
Female	Glioblastoma	2.59	2.40	2.39	2.38	2.51
	Meningioma	5.04	5.56	6.01	7.19	8.44
	Nerve Sheath	1.04	1.11	1.17	1.45	1.60
	Pituitary	0.88	0.82	0.93	1.42	2.56
	Total	**13.86**	**14.27**	**15.07**	**17.19**	**19.88**

Table 4.2. Age-adjusted incidence of selected primary CNS tumours in the sequential reports of CBTRUS by gender. Adapted from Khurana et al.[43] Rates are expressed in cases per 100,000 person-years.

Table 4.3 shows age-adjusted incidence rates by year for selected primary CNS tumours by gender. Significance trends and graphs are presented in the publications above (**Chapter 2** and **Chapter 3**) and **Appendix 6.7**. The table is included for ease of comparison of rates with the latest CBTRUS rates (**Table 4.2**).

	Current Study								
Tumour	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**
TOTAL									
Glioblastoma	3.13	3.34	3.01	3.33	2.95	3.52	3.33	3.75	3.86
Meningioma	2.05	2.82	2.70	3.02	3.03	2.82	3.20	2.71	2.78
Schwannoma	0.69	0.97	0.77	0.79	0.78	0.79	0.61	0.64	0.65
Pituitary	1.43	1.48	1.39	1.59	1.68	1.17	1.66	1.36	1.26
Total	**9.95**	**11.66**	**11.28**	**12.47**	**11.75**	**11.06**	**11.99**	**11.78**	**11.94**
MALE									
Glioblastoma	4.03	4.04	3.97	4.05	4.02	4.70	3.68	4.90	4.97
Meningioma	1.14	1.42	1.36	1.55	1.81	1.81	1.73	1.85	1.78
Schwannoma	0.54	0.89	0.72	0.68	0.73	1.04	0.62	0.65	0.58
Pituitary	1.42	1.59	1.99	1.60	1.91	1.15	1.79	1.70	1.50
Total	**9.96**	**11.42**	**11.85**	**11.96**	**11.96**	**12.08**	**11.21**	**12.59**	**12.34**
FEMALE									
Glioblastoma	2.27	2.72	2.18	2.67	2.02	2.40	2.98	2.71	2.79
Meningioma	2.94	4.18	4.05	4.47	4.22	3.82	4.63	3.58	3.75
Schwannoma	0.81	1.05	0.82	0.91	0.82	0.55	0.60	0.62	0.71
Pituitary	1.45	1.39	0.87	1.59	1.47	1.17	1.53	1.05	1.03
Total	**9.98**	**11.93**	**10.93**	**13.02**	**11.67**	**10.10**	**12.74**	**11.10**	**11.58**

Table 4.3. Age-adjusted incidence of selected primary CNS tumours by year and gender. Rates are expressed in cases per 100,000 person-years.

Similar rates are observed for glioblastoma in the current study and latest CBTRUS data, with the exception of higher incidence rates in males in the latest years of study in the current study (~4.9 cases per 100,000 person-years) in the years 2007 and 2008. This data is not yet available from the CBTRUS database.

From **Tables 4.2 and 4.3**, we make the observation that the current study describes much lower rates for meningioma and nerve sheath tumours. The almost two fold increase in meningioma incidence, seen in US data, is thought to account for the higher overall brain tumour rates. This likely reflects US clinical and collection practice and can be reconciled with examination of the proportion of non-microscopically-confirmed tumours reported in the CBTRUS data set.

The latest CBTRUS report describes only 57% of non-malignant tumours as histologically confirmed, while 39% were confirmed radiologically.[10] Therefore, if we adjust the incidence rates presented above, similar rates of meningioma and nerve sheath tumours) are seen in the CBTRUS data and the current study.

Pituitary tumours however, do not follow this simple explanation, with CBTRUS incidence rates being considerably smaller than our observed rates. However, similar proportions by gender for all four major histological subtype incidence rates presented are observed. These crude comparisons give us confidence in our own study methodology.

As discussed in **Chapter 3**, the rates described in the current study for malignant brain tumours and for glioblastoma are similar to the latest published US, European and Australian Registry numbers (given the difference in definitions used). We thus have confidence in our own collection methodology.

With this in mind, we have observed significant increasing trends in the most common type of non-malignant brain tumour – meningioma. In Australia, we have no direct comparator for meningioma rates due to lack of mandatory collection found in Europe and the United States.

Tables 4.4 and 4.5 below compare selected histologies from historical Australian data[61] from the period 1982 through 1991 with the current study in period 2000 through 2008. It is important to recognise that these historical data were collected prior to the widespread use of imaging technology and multiple brain tumour classification changes have occurred since that time. Also, the study population between the two data sets is not the same (Victoria vs. ACT/NSW). Despite this, we observe that proportions of tumours between males and females in both data sets follow similar patterns; with higher rates of GBM seen in males but higher rates of meningioma in women, and similar rates of nerve sheath tumours between sexes.

Tumour	Males		Females	
	Number	Rates	Number	Rates
Glioblastoma multiforme	662	2.80	462	1.83
Meningioma	302	1.27	665	2.69
Nerve sheath tumour	80	0.35	83	0.35

Table 4.4 . CNS tumour incidence by histological type: age-standardised rates per 100,000 population, Victoria, Australia, 1982 – 1991. Adapted from Giles *et al.*[61]

Tumour	Males		Females	
	Number	Rates	Number	Rates
Glioblastoma multiforme	1390	4.26	885	2.53
Meningioma	515	1.61	1350	3.96
Nerve sheath tumour	233	0.72	259	0.77

Table 4.5. CNS tumour incidence by histological type: age-standardised rates per 100,000 population from the current study, 2000 - 2008. Rates have been averaged over the time period.

The numbers and rates of tumours seen in the current study are higher across the board for all tumours in both sexes. Further, the historical study covers one extra year of data when compared to the current study, and so the larger numbers and rates are further accentuated when this is taken into consideration. There are many potential explanations, some of which are discussed in **Section 4.3** below. The numbers and rates however, raise the question:

"Is the observed increased incidence rate adequately explained by factors such as collection practice, imaging technology, clinical practice and classification change?"

4.2 Demographic Features and Comparison

Age-Specific Incidence

The mean age of onset for all primary brain tumours is 53 years. However, the average age of onset for glioblastoma and meningioma, the two most common types of adult tumours (see **Table 4.6**) is about 62 years. The incidences of glioblastoma and astrocytoma peak at ages 65-74 years and then decline, while the incidence of meningioma continues to rise with increasing age.[10, 109]

Age (yr)	Most Common Histology	Second Most Common Histology
0-4	Embryonal/medulloblastoma	Pilocytic astrocytoma
5-9	Pilocytic astrocytoma	Malignant glioma, NOS
10-14	Pilocytic astrocytoma	Neuronal/glial
15-19	Pituitary	Pilocytic astrocytoma
20-34	Pituitary	Meningioma
35-44	Meningioma	Pituitary
45-54	Meningioma	Glioblastoma
55-64	Meningioma	Glioblastoma
65-74	Meningioma	Glioblastoma
75-84	Meningioma	Glioblastoma
85+	Meningioma	Neoplasm, unspecified

Table 4.6. Most common brain and CNS tumours by age. CBTRUS statistical report: NPCR and SEER data from 2004-6.[10]

Figures 4.5 and 4.6 below have been included in the discussion to aid comparison with the most up to date data from the US[9, 10] on age-specific incidence for total population for primary brain tumours and selected histologies. The CBRTUS rates shown (**Figures 4.5a) and 4.6a**)) include lymphoma amongst other histologies in incidence rates for all primary brain tumours, but comparison of meningioma, nerve sheath and pituitary tumours follow similar ICD-O-3 definitions to the current study. The definition of glioma in the CBTRUS data includes ICD-O-3 codes 9380-9384, 9391-9460, and 9480.

Incidence rates for all primary brain tumours in the 2007-8 CBRTUS report range between 4.5 and 59.9 cases per 100,000 person-years, much higher than rates described in the current study that range between 2.6 to 35.1 cases per 100,000 person-years. This reflects a variable definition and reporting practice.

Incidence rates for meningioma ranged between 0.1 and 29.2 cases per 100,000 person-years, again, much higher than the current study that found rates between 0.07 and 11.0 cases per 100,000 person-years. Rates were higher in all age groups from the US data series, but followed similar increasing rates with increasing age with the exception of patients older than 85 years (29.18 vs. 3.03 cases per 100,000 person-years). This may reflect not only variable reporting practice, but also differing clinical practice.

Rates for nerve sheath tumours were also smaller than those reported in the CBTRUS data series for all age groups. The CBTRUS data set however, does also include malignant neoplasms of the cranial and spinal nerves, likely accounting for some of the higher observed rates.

Pituitary tumours followed a similar distribution in the current study when compared to the CBTRUS data. Incidence rates ranged between 0.13 and 4.69 cases per 100,000 person-years for US data and between 0.0 and 5.3 cases per 100,000 person-years for the current study with peak incidence in both datasets in the 55-64 year age groups.

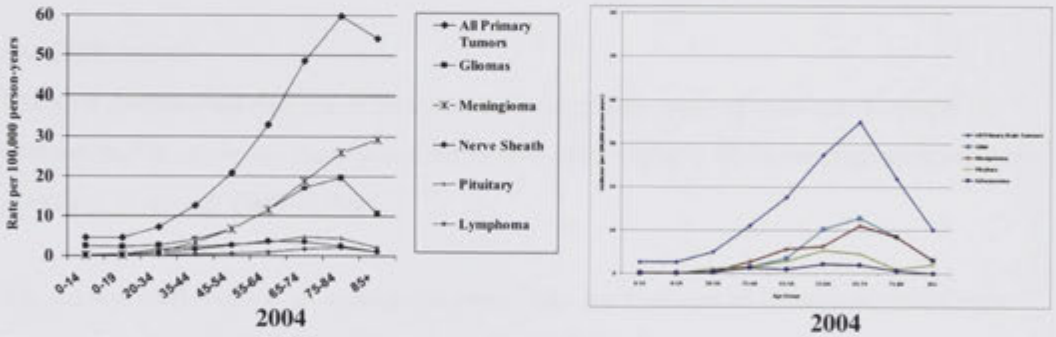


Figure 4.5. **a)** Age-specific incidence of primary brain and CNS tumours by selected histologies. CBTRUS Supplement –2004 data.[9] **b)** Current study age-specific incidence of primary brain tumours by selected histologies for total population in the year 2004.

The latest CBTRUS data reports incidence rates in the years 2004-2006 (**Figure 4.6.a**)). I have included age-specific incidence rates for all primary brain tumours and selected histologies for the year 2006 below (**Figure 4.6.b**)) as well as for our latest year 2008 (**Figure 4.6.c**)). The trends described above apply to these data and likely reflect discrepancy between reporting practice and health care delivery between the two countries.

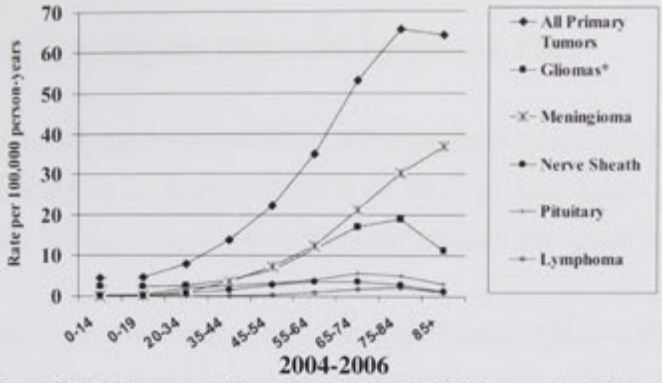
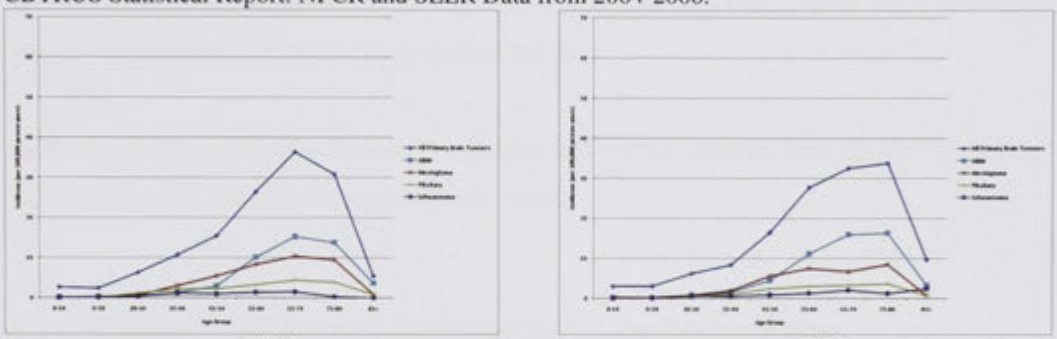


Figure 4.6. a) Age-Specific Incidence of Primary Brain and CNS Tumours by Selected Histologies. CBTRUS Statistical Report: NPCR and SEER Data from 2004-2006.[10]



2006 **2008**

Figure 4.6b) and c). Current study age-specific incidence of primary brain tumours by selected histologies for total population in the years (**b)** 2006 and **c)** 2008).

Sex Differences

It is well documented that sex differences exist for certain types of tumours. Tumours of neuroepithelial origin are more prevalent in men (40% higher), while meningiomas are more prevalent in women (80% higher).[45, 110]

The current study reports an average incidence rate for Tumours of Neuroepithelial Origin between the years 2000-2008 of 7.3 cases per 100,000 person-years in males and 4.9 cases per 100,000 person-years in females, a 49% higher rate in males.

Average incidence rates across the years 2000-2008 for meningioma for males and females were 1.6 and 3.9 cases per 100,000 person-years respectively. This calculates to a 146% higher rate in females.

The observed incidence rates by gender from the current study are thus proportionally akin to published international rates.

4.3 Factors Influencing the Observed Incidence Rate

Multiple factors have influenced our estimation of the incidence rate of primary brain tumours in the ACT and NSW region in the period 2000-2008. Some of these factors will have had more influence than others, but we have attempted to control for each one where possible.

As discussed previously, inherent in our collection methodology and our definition of a primary brain tumour, we have introduced a certain degree of error in our estimation of the incidence rate (see *Chapter 1.5 Sampling*). Specifically, sourcing and data matching of cases limited by ethical constraints has proved a considerable hurdle.

Rather than re-iterating these points, this section will discuss broader issues related to brain tumour diagnosis, classification and capture rates.

4.3.1 Clinical Practice and its Influence on Incidence Rates

Marked changes in the clinical practice and management of central nervous system tumours have occurred over the past 30-40 years.

Notably, better diagnostic capability through clinician awareness and improved imaging technology, as well as safer anaesthetic and surgical practice, and better treatment modalities such as chemotherapy and radiotherapy have revolutionised brain tumour diagnosis and management.[111, 112] These improvements have presumably resulted in increased incidence rates based on histological diagnosis.

At the same time, the increase in accuracy of diagnostic imaging as well as palliative care referrals would presumably offset some of the increase in brain tumour incidence related to increasing surgery rates, with some patients declining the option for surgical excision.

A large study examining 23,766 patient discharges from 1977 to 2001 at the ACT/NSW region's largest neurosurgical centre did in fact demonstrate a steady increase in mean age (9.5 years $P < 0.0001$) for CNS (astrocytic and oligodendroglial) tumour admissions from 1977 to 2002 ($n = 1339$). There was little change in the proportion of patients not receiving surgery during the study period, implying the increase in mean age was for surgical treatment of CNS tumours.[94, 113]

The study also demonstrated a decreasing trend in burr hole biopsy and a rise in all forms of craniotomy, as well as decreasing mortality and complication rates.[94, 113]

This change in clinical practice may well account for the increase in incidence of all malignant primary brain tumours in patients aged 65 years and above. No studies have looked at the individual contributing components however.

4.3.2 Imaging Technology

Many studies have attributed an observed increase in incidence of brain tumours to greater diagnostic capabilities.[11, 16, 17, 114] Many authors hypothesised that the introduction of CT imaging technology in the 1970s and 1980s was a major contributing factor to the observed increasing incidence of brain tumours (particularly in the elderly population), and further influenced by the later introduction of widespread MR imaging technology use. Others however, argued that improved imaging technology only partially explained the observed increase in incidence in brain tumours, particularly in patients where malignant brain tumours become quickly apparent clinically (e.g. in children).[115]

A retrospective review of 215 patients diagnosed with malignant brain tumour between 1985 and 1989 by Desmeules and colleagues, excluded CT and MRI information from patients' medical records and suggested that the diagnosis would have been made in 80% of cases irrespective of imaging.[116] They suggested the observed increase in brain tumour incidence rates observed at that time was only partly explained by the increased use of imaging technology.

The use of CT and MRI technology became widespread in Australia during the late 1980s and early 1990s, only 5-10 years behind the US and Europe.

Interestingly, as mentioned in Chapter 2, no step increase in malignant brain tumour incidence rates has been observed by the AIHW (Australia's gold standard) during the time period corresponding to CT and MR imaging introduction. The reasons for this are not entirely clear.

Most Australian studies[6, 20, 21] examining brain tumours incidence were published in the 1990s, a period presumably influenced by improved imaging diagnosis. No dramatically significant trends in incidence were reported in these studies and few have been published since. Instead, Australian brain tumour data is now almost exclusively reported by state-based registries and the AIHW.

Difficulties in classification with imaging technology are many. Diagnosis of an intracranial lesion relies on whether the lesion is intra- or extra-axial (i.e. arising from the brain itself or from surrounding structures such as the meninges), the age of the patient, contrast enhancement characteristics and location (i.e. supra- or infra-tentorial).

Metastatic disease is often difficult to differentiate between a primary tumour and clinical correlation is often needed. Contrast enhancement in a brain lesion is useful to delineate Grade I and IV tumours given classical imaging findings, but is poor at differentiating intermediate grade tumours. Meningioma is the most common extra-axial tumour, and so features high on the differential diagnosis list. Imaging diagnosis is not always reliable however, and differential diagnoses such as dural-based metastasis, solitary fibrous tumour, haemangiopericytoma, infection and post-operative change are amongst the differential diagnoses. Medulloblastoma and ependymoma are also difficult diagnoses to delineate based purely on imaging findings.

The latest WHO Classification of Tumours of the Central Nervous System (2007) introduced 8 new neoplasms and 4 variants.[117] A recent review of the neuroimaging diagnosis of these entities suggests it is possible to differentiate a few of these entities based purely on imaging alone.[118] The authors concluded however, that these entities are "uncommon and often indistinguishable from statistically more common entities."

Because of these difficulties, tissue diagnosis remains the mainstay of brain tumour delineation and histological confirmation is a must.

Expansion to notifications based on imaging diagnosis would increase case capture rate but the resources involved in such an undertaking would be immense. In addition, whether or not these diagnoses are clinically relevant is another consideration. For example, an asymptomatic meningioma diagnosed on CT or MR may be present for years with histological confirmation only being performed at autopsy (which is also uncommon currently in Australia).

Assuming a clear indication for surgery, this argues that the non-malignant brain tumours such as meningioma in the current study are more clinically relevant than those missed through lack of capture via other sources of diagnosis.

4.3.3 Collection Solely of Pathology Data

The current study has sourced data directly from pathology departments – the site of definitive diagnosis. We were interested in accurate histological subtype information not found in

Australian literature, as well as setting a baseline incidence rate for benign brain tumours, particularly meningioma and vestibular Schwannoma.

The sole use of microscopically-confirmed tumours, although providing accurate diagnosis, is not without its shortcomings. These shortcomings relate to inadequate tissue for diagnosis (e.g. from biopsy rather than excision), lack of independent review by dedicated neuropathologists and an underestimation of the true incidence rate through incomplete capture rate. Australian registries also depend on the same data and would thus experience the same shortcomings, but these are accentuated by the additional problem of late ascertainment (of which the current is relatively free).

Histological classification and grading of brain tumours has been affected by changes over time in techniques for operative sampling of tumours (see *4.3.4 Change Over Time in Classification*). Samples taken at biopsy are not necessarily representative of the whole tumour, particularly when a single small sample is taken at needle biopsy (sampling error). The introduction of stereotactic biopsy has served to increase the accuracy in targeting lesions. However, the decision of which portion of the tumour to sample and the number of samples taken is sometimes only made at the time of operation and is dependent on various peri-operative factors. Smaller tissue samples have the potential for under-grading the lesion.[119] Further, many patients undergo adjuvant radiotherapy to shrink the tumour pre-operatively. This can cause difficulties in microscopic diagnosis – distinguishing between intrinsic tumour necrosis and radiation-induced necrosis is not always possible.[119]

Importantly, omission of other sources of brain tumour diagnosis such as diagnostic imaging, radiation oncology, neurology clinics, medical oncology, autopsy reports, freestanding radiation therapy, MRI, gamma/cyber knife, and oncology centres, produces a tendency to underestimate the true incidence of brain tumours. This is particularly true of patients with slow-growing, inoperable, incidental or palliative brain tumours that do not undergo surgery. Patients with multiple co-morbidities and polypharmacy, or small meningiomas that will have minimal clinical significance have been missed by this study. A Nordic study[75] by Johannesen *et al.*, 2004 highlights this issue when considering microscopic confirmation and numbers of tumours diagnosed at autopsy. Of the 1409 patients that underwent autopsy, 358 brain tumours (3.8%) were diagnosed incidentally. The majority of these were tumours of meninges (232 cases), tumours of neuroepithelial tissue (61 cases) and tumours of the sellar region (31 cases). As mentioned above, capture of these tumours, although useful for completeness, have minimal clinical significance.

Future studies will need to address the issue of capture rate of non-histologically confirmed tumours. An important question we have hoped to raise is the question;

"How should we best capture accurate and timely brain tumour incidence rates?"

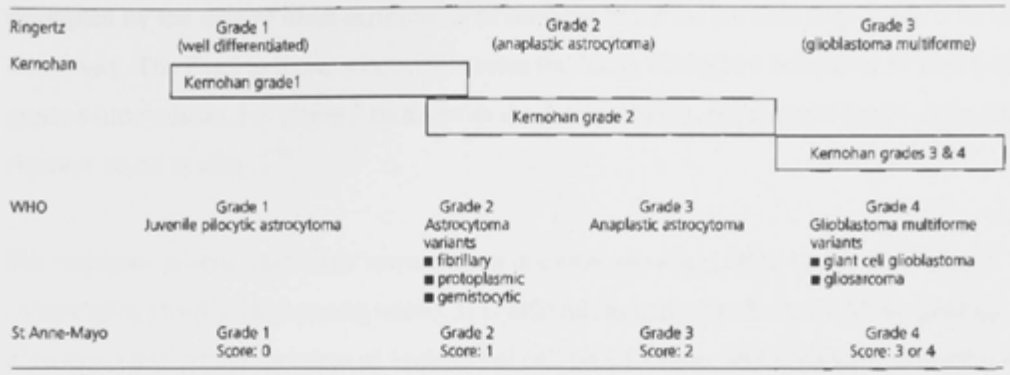
4.3.4 Change Over Time in Classification

Initially, our study collected data from all participating centres from the years 1994 to 2008 but found data completeness only from mid-1999. Although effectively halving our ability to examine incidence trends, this did allow us to be mostly free of brain tumour classification changes. After the year 2000, the majority of Australian pathologists and hospital coding systems were in line with the WHO and SNOMED grading systems [personal communication Dr Morey, St Vincent's Hospital, Department of Pathology, April 2009]. I include a historical discussion here on classification changes for completeness.

Grading Systems

Harvey Cushing, under the supervision of Percival Bailey, is generally considered the grandfather of modern neuropathology. Through collection of more than 2,000 cases of verified brain tumours, Bailey and Cushing were able to construct a classification system of gliomas based on histogenesis. Since then, the grading of glial tumours, astrocytoma in particular, has continued to be a source of debate in neuropathology. Much of the controversy surrounding the grading of these tumours relates to the distinction between grade II and III tumours. These tumours are not well differentiated on imaging alone, further clouding the issue. The essential aim of grading a tumour is to provide clinical guidance to neurosurgeons and oncologists regarding best management and prognosis.

It is important to understand changes in brain tumour classification over time, and to recognise that individual pathologists will describe the same tumour in different ways depending on their level of expertise and education. Attempts at standardisation of method are further hampered by workforce shortages where pathologists do not have the resources to precisely code tumours to TNM (tumour, node, metastasis) coding [personal communication Dr Morey, St Vincent's Hospital, Department of Pathology]. Four major classification systems have existed in the last two decades relating to brain tumours including Ringertz,[120] Kernohan,[121] St Anne-Mayo,[122] World Health Organisation (WHO).[81] The Ringertz system is a three-tiered system, while the Kernohan, WHO and St Anne-Mayo schemes use four (see **Table 4.7**).



Boxes indicate overlap between the Kernohan 4-tier and Ringertz 3-tier systems. The Ringertz, Kernohan and St Anne-Mayo systems do not grade juvenile pilocytic astrocytoma whereas the WHO system regards this as Grade 1.

Table 4.7. Summary of the four common histopathology-based grading schemes.[119]

In 1949, Kernohan and colleagues classified glial tumours into astrocytoma, ependymoma, oligodendroglioma, neuroastrocytoma and medulloblastoma. The Kernohan grade defines progressive malignancy of astrocytomas as follows:

- **Grade 1** tumours are benign astrocytomas.
- **Grade 2** tumours are low-grade astrocytomas.
- **Grade 3** tumours are anaplastic astrocytomas.
- **Grade 4** tumours are glioblastoma multiforme.

Reports in the 1980s noted an association between tumour necrosis, aggressive behaviour and decreased survival in patients with astrocytoma graded by the Ringertz system.[123] This prompted the formation of a new four-tiered system (St Anne-Mayo) that was based on a scoring system, and thus less subjective (particularly for intermediate grade tumours).

The St. Anne-Mayo grade is used to grade astrocytomas using four morphologic criteria to assign a grade: nuclear atypia, mitosis, endothelial proliferation, and necrosis. The St. Anne-Mayo grade has four categories of tumours:

- **Grade 1** tumours do not meet any of the criteria.
- **Grade 2** tumours meet one criterion, usually nuclear atypia.
- **Grade 3** tumours meet two criteria, usually nuclear atypia and mitosis.
- **Grade 4** tumours meet three or four of the criteria.

At the other end of the spectrum (i.e. low grade tumours) however, tumours that lack the features of nuclear atypia, mitosis, endothelial proliferation, and necrosis, behave less aggressively. Accurately predicting survival time, however, is difficult for tumours graded as intermediate on light microscopic features. They usually show an easily recognizable increase in tumour cell density compared with low grade tumours and have the additional features of nuclear pleomorphism, mitotic figures and vascular endothelial cell proliferation but lack necrosis.[119] "The move from a 4-tier (Kernohan) to a 3-rier (Ringertz) grading scheme was

prompted by the lack of clear differences in survival times for patients with grade 3 versus grade 4 tumours. The need to more accurately assess the likely biological behaviour of intermediate grade astrocytomas, i.e. grade 2 tumours in the 3-tier scheme, engendered the St Anne-Mayo features score system."[119]

For example, juvenile pilocytic astrocytoma is a slow growing, often cystic astrocytoma occurring in children and young adults. It is difficult to apply the St Anne-Mayo grading scheme to this tumour because of endothelial cell proliferation, and is better classified under the WHO system as a Grade I tumour. Of note, the CBTRUS still codes pilocytic astrocytoma as a malignant tumour,[10] a practice that diverges from the current study.

The WHO grade has four categories of tumours:

- **Grade I** tumours are slow-growing, non-malignant, and associated with long-term survival.
- **Grade II** tumours are relatively slow-growing but sometimes recur as higher grade tumours. They can be non-malignant or malignant.
- **Grade III** tumours are malignant and often recur as higher grade tumours.
- **Grade IV** tumours reproduce rapidly and are very aggressive malignant tumours.

We have used this classification system in the current study. A summary of significant changes in the WHO 2007 brain tumours classification are presented in **Table 4.8** below.

Grading Changes
• Anaplastic oligoastrocytomas with necrosis: now designated glioblastoma with oligodendroglial component, WHO grade IV. • Brain invasion by a meningioma: now an independent criterion for WHO grade II. • Atypical choroid plexus papilloma: criteria defined with designation of WHO grade II. • Pineocytoma: now classified as WHO grade I; pineal parenchymal tumor of intermediate differentiation: now WHO grade II or III; pineoblastoma remains WHO grade IV. • Gangliogliomas: classified as WHO grade I or III; grade II designation has been eliminated. • Cerebellar liponeurocytoma: now designated WHO grade II tumor. • Anaplastic hemangiopericytoma, WHO grade III: criteria established for distinguishing from hemangiopericytoma, WHO grade II.
New Entities, Variants, Patterns of Differentiation, and Syndromes
• Angiocentric glioma, WHO grade I • Pituicytoma, WHO grade I • Spindle cell oncocytoma of the adenohypophysis, WHO grade I • Papillary glioneuronal tumor, WHO grade I • Rosette-forming glioneuronal tumor of the fourth ventricle, WHO grade I • Pilomyxoid astrocytoma, WHO grade II • Extraventricular neurocytoma, WHO grade II • Papillary tumor of the pineal region, WHO grades II–III • Glioneuronal tumor with neuropil-like islands, WHO grades II–III • Small cell glioblastoma, WHO grade IV • Rhabdoid tumor predisposition syndrome
Other Classification Changes
• Medulloblastoma: variants include large cell, anaplastic, extensive nodularity, and desmoplastic/nodular; myogenic differentiation (previously medullomyoblastoma) and melanotic differentiation (previously melanotic medulloblastoma) are now considered morphologic patterns. • CNS PNETs: reorganized to include CNS/supratentorial PNET (including neuroblastomas and ganglioneuroblastomas), medulloepithelioma, and ependymoblastoma. • Giant cell glioblastoma and gliosarcoma: now classified variants of glioblastoma. • Hemangioblastoma: now has its own chapter as an entity, apart from von Hippel-Lindau disease. • Olfactory neuroblastoma and peripheral neuroblastomas: no longer included in the CNS classification.

Table 4.8. Significant Changes in the World Health Organization (WHO) 2007 CNS Tumour Classification. CNS indicates central nervous system; PNET, primitive neuroectodermal tumour. Taken from Brat 2008.[124]

As an example, in the current study, we have reported a small number of new entities described in the latest WHO classification of tumours of the CNS including papillary tumour of the pineal region, pilomyxoid astrocytoma, angiocentric glioma, pituicytoma, papillary glioneuronal tumours, rosette-forming glioneuronal tumour of the fourth ventricle. These are new entities not previously included in other studies. Of these, we described only 2 cases of pilomyxoid astrocytoma, 1 case of angiocentric glioma and 3 cases of papillary glioneuronal tumours in the current study. Encountering these tumours highlights the variable uptake of new classification systems, and their employment in brain tumour databases. This issue exists not only between population-based databases, but at the individual pathologist level, depending on level of expertise and education, creating variability in incidence rates (however small).

Paediatric tumours

Paediatric tumours have traditionally been even more difficult to classify and grade, with some tumours looking aggressive microscopically, but clinically behave as non-aggressive entities. A recent publication suggested that histological diagnosis as not being a significant prognostic indicator as compared to molecular markers in paediatric high grade glioma.[125]

Medulloblastoma is increasingly recognised as a heterogenous entity and the 2007 WHO publication recognises four variants; desmoplastic/nodular, medulloblastoma with extensive nodularity, anaplastic medulloblastoma and large cell medulloblastoma, on the basis of their histopathological features. Desmoplastic/nodular and medulloblastoma with extensive nodularity medulloblastomas in infants have a better outcome, while large cell and anaplastic medulloblastomas behave aggressively.[126] Difficulties in differentiation between medulloblastoma, PNET and atypical teratoid/rhabdoid tumours exist, and future molecular markers may help address this issue. Molecular and genetic markers are an evolving field and will help further delineate histological subtypes and their clinical implications.

As mentioned, we are relatively free from brain tumour classification changes (particularly given that we have limited our analysis to more common entities) in the time period 2000 to 2008 but understanding the uncertainty surrounding histological diagnosis is important to bear in mind when interpreting these data.

4.3.5 Reporting Delay

Reporting delay relates to the time between diagnosis and notification. Institutions quote varying durations of reporting delay and cancer statistics are continually being updated. For

example, the current reporting delay of the National Cancer Institute (NCI) is almost 2 years – cases diagnosed in 2007 were reported in November 2009 and released to the public in April 2010.[127]

A study by Clegg and colleagues[15] examined brain tumour reporting delay in nine cancer registries from the SEER database. By applying joinpoint linear regression to brain tumour case counts from 1981-1998 that were adjusted by the registries over that period, they were able to quantify the impact of reporting delay on incidence rates. This has been termed *late ascertainment*, and is inherent to all institutions collecting large volumes of data from multiple different sources. They concluded that ignoring this reporting delay error produces downwardly biased trends in incidence rates, particularly in the most recent years of diagnosis.

The current study has a lag time of approximately two years with constraints of resource and staffing shortage. We feel that collection of brain tumour data at the source of histological diagnosis however, is the most clinically appropriate method of collecting accurate and timely data for trend analysis.

4.4 Feasibility for Expansion to Nation-Wide Registry

A full summary of International, European and US registry practice is provided by Bray and Parkin.[101, 128] The authors describe issues around comparability, validity, timeliness and data completeness of cancer registry data. Expansion to a nation-wide reporting system for primary brain tumours is an enormous undertaking to say the least. We feel however, that it is both necessary and timely to assess potential risk factors for the development of such poorly differentiated and difficult to treat entities. Treatment options are few and survival poor at best. We suggest however, that this will not be possible without the passing of legal mandatory reporting practice, akin to the US experience.

Casefinding

There are many sources of potential casefinding including, but not limited to;

- Disease indices
- Surgery logs
- Diagnostic imaging
- Radiation oncology
- Neurology clinics
- Medical oncology

- Autopsy reports
- Pathology reports
- Freestanding radiation therapy centres
- Freestanding MRI centres
- Freestanding gamma/cyber knife centres
- Freestanding oncology centres
- Data exchange with other central registries
- Death clearance process

Collection of clinical information from multiple different sources would allow verification of cases as well as controlling for rare but significant disorders. For example, genetic predispositions such and neurofibromatosis are associated with pilocytic astrocytoma, meningioma and optic nerve glioma, while neurofibromatosis II is associated with meningioma. Co-ordinating multiple notification centres and providing meaningful data would be crucial.

There are certainly many sources of brain tumour data, all with relative advantages and disadvantages, but one larger question that needs to be answered is;

"Should brain tumour data collection be based on whole population mandatory reporting, or just a sample of the whole?"

Date of Diagnosis

A further complication of involving multiple sources of notification is the impact on reporting method through definition of the actual date of diagnosis issue.

The rules found in the Commission on Cancer's Facility Oncology Data Standards (FORDS),[87] Section 2: Coding Instructions, pages 89 and 90 state that it is not unusual for a patient with a non-malignant CNS tumour to be diagnosed in a physician's office and treated with watchful waiting. Several years may go by before the patient receives subsequent treatment at a health care facility in the form of surgery or radiation therapy or some type of systemic therapy. Also, non-malignant CNS tumours, especially meningiomas, often recur. The date of initial diagnosis should be recorded in the abstract, not the date of subsequent treatment or date of recurrence. Health records must be reviewed carefully to determine the initial date of diagnosis by a medical practitioner, regardless if the initial diagnosis was clinical or histologic.

The report above is published by the American College of Surgeons, while the European recommendation is shown in **Table 4.9**. This issue is a source of debate but a uniform approach is needed.

	Rules for registration of incidence date, in decreasing order of priority:
1	Date of first histological or cytological confirmation of this malignancy (with the exception of histology or cytology at autopsy). This date should be, in the following order: Date when the specimen was taken (biopsy) Date of receipt by the pathologist Date of the pathology report
2	Date of admission to the hospital because of this malignancy.
3	When evaluated at an outpatient clinic only: date of first consultation at the outpatient clinic because of this malignancy
4	Date of diagnosis, other than 1, 2 or 3
5	Date of death, if no information is available other than the fact that the patient has died because of a malignancy
6	Date of death, if the malignancy is discovered at autopsy
Note:	Whichever date is selected, the date of incidence should not be later than the date of the start of the treatment, or decision not to treat, or date of death. The choice of incidence does not determine the coding of the item 'basis of diagnosis'

Table 4.9. Standards recommended for the definitions of incidence given by the European network of cancer registries (ENCR, 1999).[101]

Coding Rules

A unified coding system is required and many of the issues were touch upon in *Chapter 1.8.3 Data Reporting Rules*. Well developed rules exist[85, 89, 95, 101, 128] and the nuances would need to be extensively discussed prior to development of a meaningful collection. Australia has many potential sources for developing a template for collection of these tumours. Following suit with the rest of the developed world would enhance the body of knowledge of primary brain tumours and potentially lead to a cure.

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Chapter 5. Conclusion

We aimed to determine the incidence in Australia with age-, sex-, and benign-versus-malignant histology-specific analyses from the relatively heterogenous populations of New South Wales (NSW) and the Australian Capital Territory (ACT).

The overall US-standardised incidence of primary brain tumours was 11.3 cases per 100,000 person-years (+0.13; 95% CI, range 9.8–12.3, n = 7651) during the study period with no significant linear increase. A significant increase in primary malignant brain tumours from 2000 to 2008 was observed; and appeared to be largely due to an increase in malignant tumour incidence in the ≥65-year age group.

A significant increasing incidence in glioblastoma multiforme (GBM) was observed, particularly after 2006. In GBM patients in the ≥65-year group, significantly increasing incidence for men and women combined and men only were seen. Rising trends in incidence were also seen in meningioma for total male population and males aged 20-64 years but Australia has relatively non-changing low rates for meningioma compared to the US, which also has significant rises in overall rates, possibly explained by the large increases in meningioma rates. Significantly decreasing incidence trends were observed for Schwannoma for the total study population, significant in women but not men.

This collection represents the most contemporary data on primary brain tumour incidence in Australia. Whether the observed increase in malignant primary brain tumours, particularly in persons aged ≥65 years, is due to improved detection, diagnosis, and care delivery or a true change in incidence remains undetermined. Our registries may observe an increase in malignant tumours in the next few years that they are not detecting now due to late ascertainment.

Non-malignant tumours are currently not routinely monitored in Australia. Many international countries have recognised the importance of these tumours but Australia is yet to follow suit. The preliminary analysis presented in this thesis adds weight to the argument that collection of these tumours is necessary.

We recommend a direct, uniform and centralized approach to monitoring primary brain tumour incidence, including the introduction of non-malignant data collection.

Chapter 6. Appendices

6.1 Overview of Tumours of the Central Nervous System

Malignant brain tumours are a rare occurrence, accounting for approximately 2% of all cancer in adults. The greatest proportion of adult tumours are supratentorial, occurring in the cerebral hemispheres, and the majority (86%) arise from glial cells. Despite its relative rarity the burden of these tumours is considerable for the individuals, their families, and the health care system.[47] Poor survival rates lead to a disproportionate number of years of life lost (~21 years of life lost on average) compared to other cancers.[129]

The central nervous system refers to the brain and spinal cord, whereas the peripheral nervous system refers to nerves exiting from the spinal cord to control the body. The central and peripheral nervous systems are a continuous system, giving and receiving feedback from each other. The current study is primarily interested in brain tumours that have originated in the brain parenchyma (substance) itself, termed primary brain tumours. Secondary brain tumours, which originate from elsewhere in the body and metastasize to the brain are the most common type of brain tumour. These were not included in our study.

As mentioned previously, although primary brain tumours may be split into malignant and non-malignant entities, the distinction in terms of clinical effect is blurred when considering intra-cranial neoplasms. The finite volume of the intra-cranial compartment means that even benign tumours can have deleterious effects depending on location and size. Moreover, the anatomic site of brain tumours plays an important role in prognosis and treatment options.

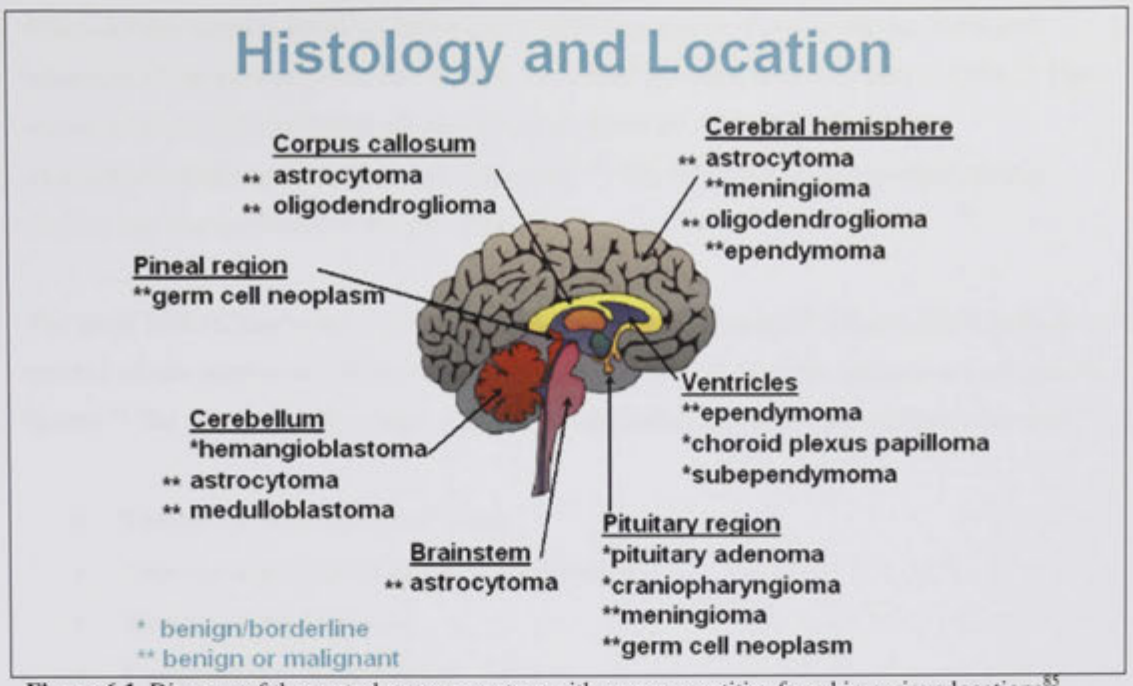


Figure 6.1. Diagram of the central nervous system with common entities found in various locations[85]

Anatomic site of brain tumours were defined as per ICD-O-3 primary site codes for (for a full listing, see Chapter 1.5.3);

Meninges	C70.0 – C70.9
Brain	C71.0 – C71.9
Cranial nerves	C72.4 – C72.9
Pituitary and pineal gland	C75.1 – C75.3

Primary brain tumours are classified by light microscopy according to their predominant cell type and graded based upon the presence or absence of standard pathologic features. Historical attempts at classifying brain tumours date back to the 1830s.[130] **Table 6.1** below simply describes the relationship between a tumour and the cell from which it formed.

Cell/Tissue of Origin	Cell/Tissue Function	Tumour Type
Astrocyte	Structural/supportive	Astrocytoma
Oligodendrocyte	Form myelin in the CNS	Oligodendroglioma
Lymphocyte	Immune mediation	Primary CNS lymphoma
Meningothelial	Surround/protect brain	Meningioma
Primitive neuronal and/or glial	Structural/supportive	Medulloblastoma

Table 6.1. Examples of Primary Brain Tumours and Their Cell or Tissue of Origin. Adapted from Doolittle.[131]

A number of classifications of brain tumours exist including the Kernohan (1950),[121] Ringertz (1950),[120] St Anne-Mayo (1993),[122] the World Health Organisation (WHO) systems 1979, 1993, 2000, 2007. These systems are important to predict response to therapy and outcome in patients with brain tumours. Perhaps the most widely used system is the WHO classification system,

which divides tumours based on histological grade as a means of predicting the biological behaviour of the tumour.[82] The first edition was edited by Zulch and published in 1979.[132] The second edition (1993) reflected advances brought about by the introduction of immunohistochemistry into diagnostic pathology.[133] The third edition incorporated genetic profiles and was published in the year 2000.[134]

The latest WHO Classification of Tumours of the Nervous System (4th Edition 2007) includes a number of new entities and tumours based on epidemiological, clinical, imaging and prognostic factors.[81] The WHO classifies brain tumours into the following major histological subgroups:

- Tumours of Neuroepithelial Tissue
- Tumours of the Cranial and Paraspinal Nerves
- Tumours of the Meninges
- Tumours of the Sellar Region
- Lymphomas and Haematopoietic Neoplasms
- Germ Cell Tumours
- Metastatic Tumours

A brief description of the major types in each category is provided in the following sections.

6.1.1 Tumours of Neuroepithelial Tissue

- Glioblastoma Multiforme (WHO Grade IV) ICD-O 9440/3

Glioblastoma multiforme (GBM) is the most frequently occurring primary brain tumour and most malignant neoplasm, often occurring rapidly without recognizable precursor lesions. Some develop slowly from diffuse astrocytoma (WHO Grade II) or anaplastic astrocytoma (WHO Grade III). They are predominantly astrocytic in differentiation and due to their highly invasive nature, complete resection is rarely achieved, despite chemo- and radiotherapy. Less than half of patients with GBM survive more than a year (**Table 6.2**). This is particularly true for older patients.

	Brain/CNS Tumours	**GBM**
One-year survival	51.5%	29.3%
Two-year survival	37.3%	8.7%
Five-year survival	29.1%	3.3%
Ten-year survival	25.3%	2.3%

Table 6.2. Observed average relative survival rates for patients diagnosed over the period 1973-2002 with a primary malignant brain/CNS tumours vs. glioblastoma multiforme. Adapted from Accelerate Brain Cancer Cure website[135]

- Anaplastic Astrocytoma (WHO Grade III) ICD-O 9401/3

Anaplastic astrocytoma is a diffusely infiltrating malignant brain tumour that primarily affects adults. It mostly arises from the cerebral hemispheres, either from diffuse astrocytoma WHO grade II or *de novo* (i.e. without a recognizable precursor lesion). These tumours have an inherent tendency to progress to glioblastoma multiforme. The rate of progression is variable, but some studies suggest a mean time interval of two years.[136]

- Diffuse Astrocytoma (WHO Grade II) ICD-O 9400/3

Diffuse astrocytoma is a diffusely infiltrating astrocytoma typically affecting young adults and characterized by a high degree of cellular differentiation and slow growth. Depending on the predominant cellular composition of the tumour, it may be further classified into fibrillary (ICD-O 9420/3), gemistocytic (ICD-O 9411/3), and protoplasmic (ICD-O 9410/3) types. Diffuse astrocytoma represents 10-15% of all astrocytic brain tumours with mean survival time after surgical resection ranging from 6-8 years.[81] Gemistocytic astrocytoma is more prone to malignant transformation to anaplastic astrocytoma and glioblastoma multiforme,[137, 138] but the WHO Working Groups did not recommend assigning it a WHO grade III as for anaplastic astrocytoma.[81, 137]

- Oligodendroglioma (WHO Grade II) ICD-O 9450/3

These tumours are diffusely infiltrating, well-differentiated glioma of adults, and appear on light microscopy as round cells with perinuclear halos (termed the "fried egg" appearance) and an acutely branching (chicken-wire) capillary pattern. Oligodendroglioma accounts for approximately 2.5% of all primary brain tumours and 5-6% of all gliomas.[8-10, 139]

- Anaplastic Oligodendroglioma (WHO Grade III) ICD-O 9382/3

Anaplastic oligodendroglioma is a malignant brain tumour of oligodendrocytic cells that has diffuse histological features and less favourable prognosis than oligodendroglioma. This type of tumour makes up approximately 1.2% of all primary brain tumours predominantly affecting adults, with a peak incidence between ages 45 and 50.[9, 10, 139] Manifestation of anaplastic oligodendroglioma is thus 7-8 years later on average than WHO Grade II oligodendroglioma.[9, 10, 139] Recent advances in the treatment of oligodendroglioma and anaplastic oligodendroglioma through the use of chemotherapy-radiotherapy combination have lead to improved survival rates

from 3.5 years[139] to 4-5 years.[140-143] These rates are further improved in patients whose tumours have lost the 1p and 19q allele.[140, 141]

These advances are important to the current study because they introduce a potential bias to the incidence rates through increased genetic testing (1p/19q deletions), and thus diagnosis of oligodendrogliomas. It has further been suggested that less stringent diagnostic criteria triggered by a desire not to impede any patient from gaining benefit from chemotherapy has accounted for an increased incidence.[8-10, 139] A recent study using both CBTRUS and SEER data showed an inverse trend between the incidence of oligodendroglioma and astrocytoma over the period 1973-2004. In the recent years a levelling off of the observed rapid increased oligodendroglioma incidence was suggested by the authors as a return to the true incidence that was previously caused by misclassification and a desire not to deprive patients of a chance for cure.[18]

- Medulloblastoma (WHO Grade IV) ICD-O 9470/3

Medulloblastoma is a malignant embryonal tumour of the cerebellum found predominantly in children. It is invasive in nature with an inherent tendency to metastasize to other sites via cerebrospinal fluid pathways. A number of types exist, including desmoplastic/nodular medulloblastoma (ICD-O 9471/3), medulloblastoma with extensive nodularity (ICD-O 9471/3), anaplastic medulloblastoma (ICD-O 9474/3), and large cell medulloblastoma (ICD-O 9474/3). Annual incidence has been estimated at 0.5 per 100 000 children less than 15 years of age,[8-10, 144] with a peak age at 7 years and a male predominance of 65%. Seventy percent of medulloblastomas occur in patients less than 16 years[145, 146] and rarely occur beyond the fifth decade of life. A recent study highlighted the seasonal variation in incidence of paediatric medulloblastoma in the US over the period 1995-2001.[147]

6.1.2 Tumours of Cranial Nerves

- Vestibular Schwannoma (WHO Grade I) ICD-O 9560/0

A Schwannoma is a benign nerve sheath tumour that is typically encapsulated and well-differentiated. These can occur in any nerve sheath. Multiple Schwannomas are associated with neurofibromatosis type 2 or Schwannomatosis. The vast majority of Schwannomas occur outside the central nervous system, but we have limited our focus only to intra-cranial Schwannomas. They represent 8% of intra-cranial tumours and 85% of cerebellopontine angle tumours.[81] When Schwannomas occur in the eighth cranial nerve they are termed vestibular Schwannoma or acoustic neuroma and typically present asymptomatically or with hearing loss.

These tumours have recently become the focus of extensive research to determine whether a positive link exists between mobile phone usage and development of the tumour. Some authors report positive associations,[43, 55, 56, 58, 68, 148, 149] while others refute the association.[71, 73]

6.1.3 Tumours of the Meninges

- Meningioma (WHO Grade I-III) ICD-O 9530/0

Most meningiomas are benign and correspond to WHO Grade I (**Table 6.3**). They are neoplasms of the meningothelial (arachnoidal) cells that form the covering of the brain substance (dura). They account for 24-40% of all primary intra-cranial tumours,[10, 150] although many are found incidentally and patients may remain asymptomatic without a resection for many years.

Meningioma with low risk of recurrence and aggressive growth		
		ICD-O code
Meningioma	Who Grade I	9530/0
Meningothelial meningioma	Who Grade I	9531/0
Fibrous (fibroblastic) meningioma	Who Grade I	9532/0
Transitional (mixed) meningioma	Who Grade I	9537/0
Psammomatous meningioma	Who Grade I	9533/0
Angiomatous meningioma	Who Grade I	9534/0
Microcystic meningioma	Who Grade I	9530/0
Secretory meningioma	Who Grade I	9530/0
Lymphoplasmacyte-rich meningioma	Who Grade I	9530/0
Metaplastic meningioma	Who Grade I	9530/0
Meningioma with greater likelihood of recurrence and/or aggressive growth		
Clear cell meningioma	Who Grade II	9538/1
Chordoid meningioma	Who Grade II	9538/1
Atypical meningioma	Who Grade II	9539/1
Papillary meningioma	Who Grade III	9538/3
Rhabdoid meningioma	Who Grade III	9538/3
Anaplastic (malignant) meningioma	Who Grade III	9530/3

Table 6.3. Meningiomas grouped by likelihood of recurrence and grade. Adapted from the latest WHO Classification of Tumours of the Central Nervous System.[81]

These tumours have also recently become the focus of extensive research to determine whether a positive link exists between mobile phone usage and development of the tumour,[57] and genetic associations for targeted therapeutic options.[150] Despite the vast majority of these tumours being slow-growing, they are nonetheless clinically significant and can cause obstruction of normal

fluid flows through the brain, leading to seizures, coma and death. Meningiomas are mandated by law in the US for reporting to Cancer Registries, but this is not the case in Australia. As such, we have a limited view of the incidence of these tumours.

6.1.4 Tumours of the Sellar Region

- Pituitary Adenoma (WHO Grade I) ICD-O 8140/0

By far the most common tumour of the pituitary gland is the pituitary adenoma, comprising about 12% of all intra-cranial neoplasms. Because this tumour arises from hormone secreting cells of the pituitary, it mostly affects the endocrine system, but it can have devastating effects on the central nervous system through mass effect (compression of surrounding structures such as nerves that control vision).

6.1.5 Other Neoplasms

A number of tumours not considered in the current study include subtypes of lymphomas and haematopoietic neoplasms, germ cell tumours and metastatic tumours. With the exception of certain tumours (e.g. primary central nervous system lymphoma, haemangioma, haemangiopericytoma), this group is not considered as originating from the brain parenchyma (i.e. primary) or evolve from embryological origins.

6.2 *Migration Data Table (Australian Hospital Statistics)*

Table 6.4 below shows separation statistics for all Australian states and territories. This data is compiled by the AIHW and refers to the number of patients receiving treatment in a state or territory separate to their residential address. This data was used to determine a weighting factor of 3.21% in the current study.

	State or territory of hospitalisation									Separations per 1,000 population[b]
State or territory of usual residence	NSW	Vic	Qld	WA	SA	Tas	ACT	NT	Total	
Public hospitals										
New South Wales	1,426,157	18,897	9,120	583	1,659	247	18,075	345	1,475,083	207.8
Victoria	5,868	1,285,853	1,825	522	2,204	260	275	316	1,297,123	243.5
Queensland	12,387	1,365	768,237	443	365	193	194	367	783,551	189.9
Western Australia	456	430	394	447,508	284	78	46	1,647	450,843	218.4
South Australia	575	1,559	407	214	383,409	59	53	2,550	388,826	231.6
Tasmania	338	1,415	229	70	81	96,199	19	27	98,378	191.0
Australian Capital Territory	2,998	224	156	52	45	12	57,056	34	60,577	195.1
Northern Territory	218	314	370	231	2,044	9	12	80,527	83,725	466.4
Other Australian territories[c]	n.p.	0	4	158	0	0	1	0	n.p.	n.p.
Not elsewhere classified[d]	n.p.	4,185	3,291	1,115	65	99	36	0	n.p.	n.p.
Not reported	0	0	597	0	491	0	0	0	1,088	..
Total	**1,462,129**	**1,314,242**	**784,630**	**450,896**	**390,647**	**97,156**	**75,767**	**85,813**	**4,661,280**	**218.8**
Private hospitals										
New South Wales	790,009	6,902	25,239	204	1,390	n.p.	n.p.	n.p.	831,136	116.0
Victoria	6,523	750,610	1,555	136	1,249	n.p.	n.p.	n.p.	760,258	141.1
Queensland	3,446	950	712,880	163	213	n.p.	n.p.	n.p.	717,753	172.1
Western Australia	355	286	227	288,186	98	n.p.	n.p.	n.p.	289,225	138.4
South Australia	193	403	291	57	224,718	n.p.	n.p.	n.p.	225,716	130.3
Tasmania	273	1,120	270	30	55	n.p.	n.p.	n.p.	60,837	115.5
Australian Capital Territory	1,996	181	150	15	56	n.p.	n.p.	n.p.	29,475	92.0
Northern Territory	199	364	499	179	1,247	n.p.	n.p.	n.p.	13,528	13.4
Other Australian territories[c]	n.p.	0	83	36	0	n.p.	n.p.	n.p.	n.p.	n.p.
Not elsewhere classified[d]	n.p.	601	837	157	26	n.p.	n.p.	n.p.	n.p.	n.p.
Not reported	0	0	3	0	272	n.p.	n.p.	n.p.	275	..
Total	**808,376**	**761,417**	**742,014**	**289,163**	**229,324**	**n.p.**	**n.p.**	**n.p.**	**2,941,637**	**136.3**

(a) Separations for which the care type was reported as *Newborn with no qualified days*, and records for *Hospital boarders* and *Posthumous organ procurement* have been excluded.
(b) Rates per 1,000 population were directly age-standardised as detailed in Appendix 1.
(c) Includes Cocos (Keeling) Islands, Christmas Island, Jervis Bay Territory. Records with a *State of usual residence* of *Other Australian territories* in New South Wales are currently under review.
(d) Includes resident overseas, at sea, no fixed address. Records with a *State of usual residence* of *Not elsewhere classified* in New South Wales are currently under review.

Table 6.4: Separations, by state or territory of usual residence and hospital sector, states and territories, 2006-07. p155 Australian Hospital Statistics 2006-7, AIHW 2008.[91]

Calculation of weighting factor;

Public Hospitals

1. The number of NSW residents using public hospitals in NSW minus NSW residences using public hospitals in other Australian states, minus ACT residents using NSW public hospitals equalled 30,851 persons (1,475,083 – 1,426,157 - 18,075).
2. 30,851 + number of ACT residents going to other states for public health care (224 + 156 + 52 + 45 + 12) equals 31,340.
3. Given a total residence of ACT and NSW is 1,483,223.
4. A migration rate of 0.02113 (31,340/1,483,223) is calculated

Private Hospitals

1. The number of NSW residents using private hospitals in NSW minus NSW residences using private hospitals in other Australian states, minus ACT residents using NSW private hospitals equalled 41,127 persons (831,136 – 790,009).
2. 41,127 + number of ACT residents going to other states for public health care (181 + 150 + 15 + 56) equals 41,529.

3. Given a total residence of NSW is 790,009.
4. A migration rate of 0.052568 (41,529/790,009) is calculated

Combined totals equalled 2,273,232 (1,483,223 + 790,009) with migration of 72,869 (31,340 + 41,529) people giving a **final rate of 0.032055** (72,869/2,273,232).

6.3 Standard Population Tables

Age group	Australian Standard 2001	2000 U.S. Standard	WHO World standard 2000-2025
0-4	1282357.00	18986520.00	886000.00
5-9	1351664.00	19919840.00	869000.00
10-14	1353177.00	20056779.00	860000.00
15-19	1352745.00	19819518.00	847000.00
20-24	1302412.00	18257225.00	822000.00
25-29	1407081.00	17722067.00	793000.00
30-34	1466615.00	19511370.00	761000.00
35-39	1492204.00	22179956.00	715000.00
40-44	1479257.00	22479229.00	659000.00
45-49	1358594.00	19805793.00	604000.00
50-54	1300777.00	17224359.00	537000.00
55-59	1008799.00	13307234.00	455000.00
60-64	822024.00	10654272.00	372000.00
65-69	682513.00	9409940.00	296000.00
70-74	638380.00	8725574.00	221000.00
75-79	519356.00	7414559.00	152000.00
80-84	330050.00	4900234.00	91000.00
85+	265235.00	4259173.00	63500.00

Table 6.5. Standard population tables by five year age groups for 2001 Australian Standard Population, 2000 US standard Population, and WHO World Standard Population 2000-2025.

6.4 CBTRUS Data and Morphology Code Comparison

Histology	TOTAL N	% of All Reported Brain Tumors	Adjusted Rate	95% C.I.
Tumors of Neuroepithelial Tissue	**54,301**	**34.3**	**6.46**	**(6.41-6.52)**
Pilocytic astrocytoma	2,625	1.7	0.33	(0.31-0.34)
Protoplasmic & fibrillary astrocytoma	854	0.5	0.10	(0.10-0.11)
Anaplastic astrocytoma	3,385	2.1	0.40	(0.39-0.42)
Unique astrocytoma variants	753	0.5	0.09	(0.08-0.10)
Astrocytoma, NOS	3,695	2.3	0.44	(0.43-0.46)
Glioblastoma	27,040	17.1	3.17	(3.13-3.21)
Oligodendroglioma	2,269	1.4	0.27	(0.26-0.29)
Anaplastic oligodendroglioma	1,031	0.7	0.12	(0.12-0.13)
Ependymoma/anaplastic ependymoma	2,147	1.4	0.26	(0.25-0.27)
Ependymoma variants	798	0.5	0.10	(0.09-0.10)
Mixed glioma	1,573	1.0	0.19	(0.18-0.20)
Glioma malignant, NOS	3,516	2.2	0.43	(0.41-0.44)
Choroid plexus	351	0.2	0.04	(0.04-0.05)
Neuroepithelial	171	0.1	0.02	(0.02-0.02)
Non-malignant and malignant neuronal/glial	2,250	1.4	0.27	(0.26-0.29)
Pineal parenchymal	279	0.2	0.03	(0.03-0.04)
Embryonal/primitive/medulloblastoma	1,564	1.0	0.19	(0.18-0.20)
Tumors of Cranial and Spinal Nerves	**13,735**	**8.7**	**1.61**	**(1.59-1.64)**
Nerve sheath, non-malignant and malignant	13,733	8.7	1.61	(1.59-1.64)
Tumors of Meninges	**55,432**	**35.1**	**6.52**	**(6.47-6.57)**
Meningioma	53,455	33.8	6.29	(6.23-6.34)
Other mesenchymal, non-malignant and malignant	631	0.4	0.08	(0.07-0.08)
Hemangioblastoma	1,346	0.9	0.16	(0.15-0.17)
Lymphomas and Hematopoietic Neoplasms	**3,855**	**2.4**	**0.46**	**(0.44-0.47)**
Lymphoma	3,855	2.4	0.46	(0.44-0.47)
Germ Cell Tumors and Cysts	642	0.4	0.08	(0.07-0.09)
Germ cell tumors, cysts and heterotopias	642	0.4	0.08	(0.07-0.09)
Tumors of Sellar Region	**21,287**	**13.5**	**2.54**	**(2.50-2.57)**
Pituitary	20,131	12.7	2.40	(2.36-2.43)
Craniopharyngioma	1,156	0.7	0.14	(0.13-0.15)
Local Extensions from Regional Tumors	**156**	**0.1**	**0.02**	**(0.02-0.02)**
Chordoma/chondrosarcoma	156	0.1	0.02	(0.02-0.02)
Unclassified Tumors	**8,680**	**5.5**	**1.02**	**(1.00-1.05)**
Hemangioma	1,161	0.7	0.14	(0.13-0.15)
Neoplasm, unspecified	7,443	4.7	0.88	(0.86-0.90)
All other	76	0.0	0.01	(0.01-0.01)
TOTAL[b]	**158,088**	**100.0**	**18.71**	**(18.62-18.80)**

[a] *Rates are per 100,000 person years*
[b] *Refers to all brain tumors including histologies not presented in this table.*
Abbreviations: CBTRUS, Central Brain Tumor Registry of the United States; NPCR, CDC's National Program of Cancer Registries; SEER, NCI's Surveillance, Epidemiology and End Results program; CI, confidence interval; NOS, not otherwise specified.

Table 6.6. Distribution and incidence rates of primary (malignant and non-malignant) brain and central nervous system tumours by major histology groupings and histology, age-adjusted to the 2000 U.S. standard population; CBTRUS statistical report: NPCR and SEER, 2004-2006.[10]

CBTRUS Groupings[10]	Morphology codes in CBTRUS but not in the current study	Morphology codes common to both
Pilocytic astrocytoma		M 9421
Protoplasmic & fibrillary astrocytoma		M 9410 M 9420
Anaplastic astrocytoma		M 9401 M 9411
Unique astrocytoma variants		M 9383 M 9384 M 9424 **M 9425**
Astrocytoma, NOS		M 9400
Glioblastoma		M 9440 M 9441 M 9442
Oligodendroglioma		M 9450
Anaplastic oligodendroglioma	M 9460	M 9451
Ependymoma/anaplastic ependymoma		M 9391 M 9392 M 9393
Ependymoma variants		
Mixed glioma		M 9382
Glioma malignant, NOS		M 9380
Choroid plexus		M 9390
Neuroepithelial	M 9423	M 9381 M 9430 **M 9431** M 9444
Non–malignant and malignant neuronal/glial, neuronal and mixed	M 8680 M 8681 M 8682 M 8690 M 8693 M 9442/1c M 9491	M 9412 M 9413 M 9490 M 9493 M 9500 M 9505 **M 9506 M 9509**
Pineal parenchymal	M 9360	M 9361 M 9362
Embryonal/primitive/medulloblastoma	M 8963 M 9363 M 9472 M 9502 M 9503 M 9508	M 9470 M 9471 M 9472 M 9473 M 9474
Nerve sheath, non–malignant and malignant	M 9541 M 9561 M 9570	M 9540 M 9560
Other tumours of cranial and spinal nerves	M 9562	
Meningioma		M 9530 M 9531 M 9532 M 9533 M 9534 M 9537 M 9538 M 9539
Other mesenchymal, non–malignant and malignant	M 8324 M 8728 M 8770 M 8800 M 8801 M 8802 M 8803 M 8804 M 8805 M 8806 M 8810 M 8815 M 8824 M 8825 M 8830 M 8831 M 8850 M 8851 M 8857 M 8861 M 8890 M 8897 M 8900 M 8910 M 8920 M 8990 M 9040 M 9180 M 9210 M 9241 M 9260 M 9480 M 9535	M 9150
Haemangioblastoma		M 9161
Lymphoma	M 9590 M 9591 M 9596 M 9650 M 9651 M 9652 M 9653 M 9654 M 9655 M 9659 M 9661 M 9662 M 9663 M 9664 M 9665 M 9667 M 9670 M 9671 M 9673 M 9675 M 9680 M 9684 M 9687 M 9690 M 9691 M 9695 M 9698 M 9699 M 9701 M 9702 M 9705 M 9714 M 9719 M 9727 M 9728 M 9729 M 9731 M 9733 M 9734 M 9740 M 9741 M 9750 M 9755 M 9756 M 9757 M 9758 M 9766 M 9827 M 9861 M 9930 M 9970	M 9590
Germ cell tumours, cysts and heterotopias	M 8020 M 9060 M 9061 M 9064 M 9065 M 9070 M 9071 M 9072 M 9080 M 9081 M 9082 M 9083 M 9084 M 9085 M 9100	
Pituitary	M 8022 M 8040 M 8146 M 8190c M 8246 M 8260 M 8270 M 8271 M 8280 M 8281 M 8290 M 8300 M 8310 M 8320c M 8323 M 8333 M 8334 M 8341c	M 8140 M 8272 M 9582
Craniopharyngioma		M 9350 M 9351 M 9352
Chordoma/chondrosarcoma	M 9220 M 9231 M 9240 M 9370 M 9371 M 9372 M 9373	
Haemangioma	M 9121 M 9122 M 9123 M 9125 M 9130 M 9131M 9140	M 9120
Neoplasm, unspecified	M 8000 M 8001 M 8002 M 8003 M 8004 M 8005 M 8010 M 8013 M 8021	
All other	M 8683c M 8720 M 8811c M 8840c M 8860c M 8896c M 8980c M 9173 M 9580 M 9751 M 9752c M 9753c M 9754 M 9823c M 9837c M 9866c	

Table 6.7. Comparison of ICD-O-3/SNOMED morphology codes from CBTRUS and the current study. Highlighted codes are new entities included in the latest WHO Classification of Tumours of the Central Nervous System.

6.5 *Incidence tables from the current study*

US Std Incidence (+/- CI) by Year TOTAL	2000	2001	2002	2003	2004	2005	2006	2007	2008
TUMOURS OF NEUROEPITHELIAL TISSUE	**5.39 (±0.17)**	**5.86 (±0.18)**	**6.01 (±0.18)**	**6.50 (±0.19)**	**5.82 (±0.18)**	**5.89 (±0.18)**	**6.01 (±0.18)**	**6.69 (±0.19)**	**6.70 (±0.19)**
Pilocytic astrocytoma	0.22 (±0.04)	0.39 (±0.05)	0.32 (±0.04)	0.48 (±0.05)	0.30 (±0.04)	0.16 (±0.03)	0.29 (±0.04)	0.25 (±0.04)	0.32 (±0.04)
Protoplasmic & fibrillary astrocytoma	0.03 (±0.01)	0.04 (±0.02)	0.10 (±0.02)	0.04 (±0.02)	0.06 (±0.02)	0.06 (±0.02)	0.03 (±0.01)	0.01 (±0.01)	0.04 (±0.02)
Anaplastic astrocytoma	0.49 (±0.05)	0.54 (±0.05)	0.45 (±0.05)	0.60 (±0.06)	0.46 (±0.05)	0.45 (±0.05)	0.47 (±0.05)	0.49 (±0.05)	0.60 (±0.06)
Unique astrocytoma variants	0.08 (±0.02)	0.00 (±0.00)	0.04 (±0.02)	0.11 (±0.02)	0.03 (±0.01)	0.11 (±0.03)	0.03 (±0.01)	0.04 (±0.02)	0.06 (±0.02)
Astrocytoma, NOS	0.32 (±0.04)	0.29 (±0.04)	0.48 (±0.05)	0.40 (±0.05)	0.29 (±0.04)	0.23 (±0.04)	0.35 (±0.04)	0.49 (±0.05)	0.37 (±0.05)
Glioblastoma	3.13 (±0.13)	3.34 (±0.14)	3.01 (±0.13)	3.33 (±0.14)	2.95 (±0.13)	3.52 (±0.14)	3.33 (±0.14)	3.75 (±0.14)	3.86 (±0.15)
Oligodendroglioma	0.18 (±0.03)	0.33 (±0.04)	0.50 (±0.05)	0.45 (±0.05)	0.56 (±0.06)	0.26 (±0.04)	0.35 (±0.04)	0.33 (±0.04)	0.16 (±0.03)
Anaplastic oligodendroglioma	0.26 (±0.04)	0.26 (±0.04)	0.27 (±0.04)	0.26 (±0.04)	0.46 (±0.05)	0.27 (±0.04)	0.33 (±0.04)	0.21 (±0.03)	0.24 (±0.04)
Ependymoma/anaplastic ependymoma	0.16 (±0.03)	0.14 (±0.03)	0.15 (±0.03)	0.16 (±0.03)	0.11 (±0.02)	0.10 (±0.02)	0.15 (±0.03)	0.10 (±0.02)	0.14 (±0.03)
Ependymoma variants	0.00 (±0.00)	0.00 (±0.00)	0.00 (±0.00)	0.00 (±0.00)	0.00 (±0.00)	0.00 (±0.00)	0.00 (±0.00)	0.00 (±0.00)	0.00 (±0.00)
Mixed glioma	0.04 (±0.02)	0.01 (±0.01)	0.13 (±0.03)	0.15 (±0.03)	0.18 (±0.03)	0.11 (±0.03)	0.04 (±0.02)	0.16 (±0.03)	0.19 (±0.03)
Glioma malignant, NOS	0.02 (±0.01)	0.02 (±0.01)	0.13 (±0.03)	0.10 (±0.02)	0.06 (±0.02)	0.13 (±0.03)	0.13 (±0.03)	0.21 (±0.03)	0.22 (±0.04)
Choroid plexus	n<16								
Neuroepithelial	n<16								
Non–malignant and malignant neuronal/glial, neuronal and mixed	0.19 (±0.03)	0.17 (±0.03)	0.20 (±0.03)	0.12 (±0.03)	0.06 (±0.02)	0.21 (±0.03)	0.23 (±0.04)	0.27 (±0.04)	0.25 (±0.04)
Pineal parenchymal	n<16								
Embryonal/primitive/medulloblastoma	0.25 (±0.04)	0.26 (±0.04)	0.19 (±0.03)	0.22 (±0.04)	0.19 (±0.03)	0.23 (±0.04)	0.20 (±0.03)	0.25 (±0.04)	0.09 (±0.02)
TUMOURS OF CRANIAL AND SPINAL NERVES	**0.69 (±0.06)**	**0.97 (±0.07)**	**0.77 (±0.07)**	**0.79 (±0.07)**	**0.78 (±0.07)**	**0.79 (±0.07)**	**0.61 (±0.06)**	**0.64 (±0.06)**	**0.65 (±0.06)**
Schwannoma	0.69 (±0.06)	0.97 (±0.07)	0.77 (±0.07)	0.79 (±0.07)	0.78 (±0.07)	0.79 (±0.07)	0.61 (±0.06)	0.64 (±0.06)	0.65 (±0.06)
TUMOURS OF MENINGES	**2.18 (±0.11)**	**3.06 (±0.13)**	**2.88 (±0.13)**	**3.27 (±0.14)**	**3.16 (±0.13)**	**2.92 (±0.13)**	**3.37 (±0.14)**	**2.90 (±0.13)**	**2.96 (±0.13)**
Meningioma	2.05 (±0.11)	2.82 (±0.13)	2.70 (±0.12)	3.02 (±0.13)	3.03 (±0.13)	2.82 (±0.13)	3.20 (±0.13)	2.71 (±0.12)	2.78 (±0.12)
Other mesenchymal, non–malignant and malignant	n<16								
Haemangioblastoma	0.11 (±0.02)	0.18 (±0.03)	0.15 (±0.03)	0.19 (±0.03)	0.12 (±0.03)	0.04 (±0.02)	0.15 (±0.03)	0.17 (±0.03)	0.16 (±0.03)
LYMPHOMAS AND HEMOPOIETIC NEOPLASMS	n<16								
Lymphoma	n<16								
TUMOURS OF SELLAR REGION	**1.52 (±0.09)**	**1.60 (±0.09)**	**1.46 (±0.09)**	**1.76 (±0.10)**	**1.77 (±0.10)**	**1.28 (±0.08)**	**1.80 (±0.10)**	**1.50 (±0.09)**	**1.38 (±0.09)**
Pituitary	1.43 (±0.09)	1.48 (±0.09)	1.39 (±0.09)	1.59 (±0.09)	1.68 (±0.10)	1.17 (±0.08)	1.66 (±0.10)	1.36 (±0.09)	1.26 (±0.08)
Craniopharyngioma	0.09 (±0.02)	0.12 (±0.03)	0.07 (±0.02)	0.17 (±0.03)	0.09 (±0.02)	0.12 (±0.03)	0.15 (±0.03)	0.14 (±0.03)	0.12 (±0.03)
UNCLASSIFIED TUMOURS	**0.12 (±0.03)**	**0.15 (±0.03)**	**0.16 (±0.03)**	**0.11 (±0.02)**	**0.21 (±0.03)**	**0.14 (±0.03)**	**0.18 (±0.03)**	**0.06 (±0.02)**	**0.22 (±0.03)**
Haemangioma	0.12 (±0.03)	0.15 (±0.03)	0.16 (±0.03)	0.11 (±0.02)	0.21 (±0.03)	0.14 (±0.03)	0.18 (±0.03)	0.06 (±0.02)	0.22 (±0.03)

Total per Year	**9.95 (±0.24)**	**11.66 (±0.26)**	**11.28 (±0.25)**	**12.47 (±0.26)**	**11.75 (±0.26)**	**11.06 (±0.25)**	**11.99 (±0.26)**	**11.78 (±0.26)**	**11.94 (±0.26)**
US Std Incidence (+/- CI) by Year									
MALE	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**
TUMOURS OF NEUROEPITHELIAL TISSUE	**6.49 (±0.19)**	**7.07 (±0.20)**	**7.25 (±0.20)**	**7.59 (±0.21)**	**7.07 (±0.20)**	**7.63 (±0.21)**	**6.56 (±0.19)**	**8.09 (±0.21)**	**7.97 (±0.21)**
Pilocytic astrocytoma	0.16 (±0.03)	0.52 (±0.05)	0.34 (±0.04)	0.49 (±0.05)	0.28 (±0.04)	0.16 (±0.03)	0.23 (±0.04)	0.18 (±0.03)	0.31 (±0.04)
Protoplasmic & fibrillary astrocytoma	0.06 (±0.02)	0.03 (±0.01)	0.12 (±0.03)	0.02 (±0.01)	0.10 (±0.02)	0.06 (±0.02)	0.00 (±0.00)	0.00 (±0.00)	0.03 (±0.01)
Anaplastic astrocytoma	0.61 (±0.06)	0.67 (±0.06)	0.39 (±0.05)	0.79 (±0.07)	0.60 (±0.06)	0.43 (±0.05)	0.64 (±0.06)	0.58 (±0.06)	0.79 (±0.07)
Unique astrocytoma variants	0.06 (±0.02)	0.00 (±0.00)	0.09 (±0.02)	0.14 (±0.03)	0.06 (±0.02)	0.20 (±0.03)	0.02 (±0.01)	0.03 (±0.01)	0.03 (±0.01)
Astrocytoma, NOS	0.38 (±0.05)	0.41 (±0.05)	0.65 (±0.06)	0.34 (±0.04)	0.35 (±0.04)	0.33 (±0.04)	0.28 (±0.04)	0.64 (±0.06)	0.47 (±0.05)
Glioblastoma	4.03 (±0.15)	4.04 (±0.15)	3.97 (±0.15)	4.05 (±0.15)	4.02 (±0.15)	4.70 (±0.16)	3.68 (±0.14)	4.90 (±0.17)	4.97 (±0.17)
Oligodendroglioma	0.22 (±0.04)	0.34 (±0.04)	0.43 (±0.05)	0.60 (±0.06)	0.56 (±0.06)	0.45 (±0.05)	0.29 (±0.04)	0.49 (±0.05)	0.15 (±0.03)
Anaplastic oligodendroglioma	0.34 (±0.04)	0.28 (±0.04)	0.32 (±0.04)	0.23 (±0.04)	0.41 (±0.05)	0.37 (±0.05)	0.49 (±0.05)	0.24 (±0.04)	0.29 (±0.04)
Ependymoma/anaplastic ependymoma	0.07 (±0.02)	0.15 (±0.03)	0.12 (±0.03)	0.14 (±0.03)	0.03 (±0.01)	0.14 (±0.03)	0.21 (±0.03)	0.08 (±0.02)	0.19 (±0.03)
Ependymoma variants	0.00 (±0.00)	0.00 (±0.00)	0.00 (±0.00)	0.00 (±0.00)	0.00 (±0.00)	0.00 (±0.00)	0.00 (±0.00)	0.00 (±0.00)	0.00 (±0.00)
Mixed glioma	0.03 (±0.01)	0.03 (±0.01)	0.17 (±0.03)	0.17 (±0.03)	0.24 (±0.04)	0.14 (±0.03)	0.03 (±0.01)	0.16 (±0.03)	0.26 (±0.04)
Glioma malignant, NOS	0.03 (±0.01)	0.00 (±0.00)	0.15 (±0.03)	0.09 (±0.02)	0.03 (±0.01)	0.16 (±0.03)	0.12 (±0.03)	0.16 (±0.03)	0.15 (±0.03)
Choroid plexus	n<16								
Neuroepithelial	n<16								
Non–malignant and malignant neuronal/glial, neuronal and mixed	0.12 (±0.03)	0.21 (±0.03)	0.25 (±0.04)	0.18 (±0.03)	0.09 (±0.02)	0.28 (±0.04)	0.20 (±0.03)	0.24 (±0.04)	0.11 (±0.02)
Pineal parenchymal	n<16								
Embryonal/primitive/medulloblastoma	0.37 (±0.05)	0.34 (±0.04)	0.25 (±0.04)	0.28 (±0.04)	0.15 (±0.03)	0.21 (±0.03)	0.33 (±0.04)	0.28 (±0.04)	0.12 (±0.03)
TUMOURS OF CRANIAL AND SPINAL NERVES	**0.54 (±0.06)**	**0.89 (±0.07)**	**0.72 (±0.06)**	**0.68 (±0.06)**	**0.73 (±0.06)**	**1.04 (±0.08)**	**0.62 (±0.06)**	**0.65 (±0.06)**	**0.58 (±0.06)**
Schwannoma	0.54 (±0.06)	0.89 (±0.07)	0.72 (±0.06)	0.68 (±0.06)	0.73 (±0.06)	1.04 (±0.08)	0.62 (±0.06)	0.65 (±0.06)	0.58 (±0.06)
TUMOURS OF MENINGES	**1.17 (±0.08)**	**1.60 (±0.09)**	**1.65 (±0.10)**	**1.83 (±0.10)**	**1.98 (±0.11)**	**1.90 (±0.10)**	**1.96 (±0.10)**	**2.06 (±0.11)**	**2.02 (±0.11)**
Meningioma	1.14 (±0.08)	1.42 (±0.09)	1.36 (±0.09)	1.55 (±0.09)	1.81 (±0.10)	1.81 (±0.10)	1.73 (±0.10)	1.85 (±0.10)	1.78 (±0.10)
Other mesenchymal, non–malignant and malignant	n<16								
Haemangioblastoma	0.03 (±0.01)	0.15 (±0.03)	0.27 (±0.04)	0.19 (±0.03)	0.14 (±0.03)	0.06 (±0.02)	0.21 (±0.03)	0.21 (±0.03)	0.21 (±0.03)
LYMPHOMAS AND HEMOPOIETIC NEOPLASMS	n<16								
Lymphoma	n<16								
TUMOURS OF SELLAR REGION	**1.51 (±0.09)**	**1.72 (±0.10)**	**2.07 (±0.11)**	**1.69 (±0.10)**	**1.97 (±0.11)**	**1.30 (±0.09)**	**1.93 (±0.10)**	**1.78 (±0.10)**	**1.60 (±0.09)**
Pituitary	1.42 (±0.09)	1.59 (±0.09)	1.99 (±0.11)	1.60 (±0.09)	1.91 (±0.10)	1.15 (±0.08)	1.79 (±0.10)	1.70 (±0.10)	1.50 (±0.09)
Craniopharyngioma	0.09 (±0.02)	0.13 (±0.03)	0.08 (±0.02)	0.09 (±0.02)	0.06 (±0.02)	0.15 (±0.03)	0.14 (±0.03)	0.08 (±0.02)	0.10 (±0.02)
UNCLASSIFIED TUMOURS	**0.18 (±0.03)**	**0.14 (±0.03)**	**0.15 (±0.03)**	**0.14 (±0.03)**	**0.21 (±0.03)**	**0.18 (±0.03)**	**0.12 (±0.03)**	**0.00 (±0.00)**	**0.17 (±0.03)**
Haemangioma	0.18 (±0.03)	0.14 (±0.03)	0.15 (±0.03)	0.14 (±0.03)	0.21 (±0.03)	0.18 (±0.03)	0.12 (±0.03)	0.00 (±0.00)	0.17 (±0.03)
Total per Year	**9.96 (±0.24)**	**11.42 (±0.25)**	**11.85 (±0.26)**	**11.96 (±0.26)**	**11.96 (±0.26)**	**12.08 (±0.26)**	**11.21 (±0.25)**	**12.59 (±0.27)**	**12.34 (±0.26)**

US Std Incidence (+/- CI) by Year

FEMALE	2000	2001	2002	2003	2004	2005	2006	2007	2008
TUMOURS OF NEUROEPITHELIAL TISSUE	**4.34 (±0.17)**	**4.71 (±0.18)**	**4.91 (±0.18)**	**5.49 (±0.19)**	**4.74 (±0.18)**	**4.22 (±0.18)**	**5.46 (±0.18)**	**5.37 (±0.19)**	**5.47 (±0.19)**
Pilocytic astrocytoma	0.29 (±0.04)	0.25 (±0.05)	0.29 (±0.04)	0.48 (±0.05)	0.33 (±0.04)	0.16 (±0.03)	0.36 (±0.04)	0.32 (±0.04)	0.33 (±0.04)
Protoplasmic & fibrillary astrocytoma	0.00 (±0.01)	0.06 (±0.02)	0.09 (±0.02)	0.05 (±0.02)	0.03 (±0.02)	0.07 (±0.02)	0.07 (±0.01)	0.03 (±0.01)	0.06 (±0.02)
Anaplastic astrocytoma	0.36 (±0.05)	0.41 (±0.05)	0.49 (±0.05)	0.40 (±0.06)	0.35 (±0.05)	0.48 (±0.05)	0.29 (±0.05)	0.39 (±0.05)	0.41 (±0.06)
Unique astrocytoma variants	0.10 (±0.02)	0.00 (±0.00)	0.00 (±0.02)	0.08 (±0.02)	0.00 (±0.01)	0.02 (±0.03)	0.03 (±0.01)	0.06 (±0.02)	0.09 (±0.02)
Astrocytoma, NOS	0.26 (±0.04)	0.17 (±0.04)	0.30 (±0.05)	0.45 (±0.05)	0.24 (±0.04)	0.12 (±0.04)	0.41 (±0.04)	0.33 (±0.05)	0.27 (±0.05)
Glioblastoma	2.27 (±0.13)	2.72 (±0.14)	2.18 (±0.13)	2.67 (±0.14)	2.02 (±0.13)	2.40 (±0.14)	2.98 (±0.14)	2.71 (±0.14)	2.79 (±0.15)
Oligodendroglioma	0.13 (±0.03)	0.33 (±0.04)	0.58 (±0.05)	0.31 (±0.05)	0.55 (±0.06)	0.08 (±0.04)	0.40 (±0.04)	0.18 (±0.04)	0.17 (±0.03)
Anaplastic oligodendroglioma	0.18 (±0.04)	0.24 (±0.04)	0.23 (±0.04)	0.29 (±0.04)	0.51 (±0.05)	0.16 (±0.04)	0.17 (±0.04)	0.18 (±0.03)	0.19 (±0.04)
Ependymoma/anaplastic ependymoma	0.25 (±0.03)	0.13 (±0.03)	0.19 (±0.03)	0.19 (±0.03)	0.18 (±0.02)	0.05 (±0.02)	0.09 (±0.03)	0.11 (±0.02)	0.09 (±0.03)
Ependymoma variants	0.00 (±0.00)	0.00 (±0.00)	0.00 (±0.00)	0.00 (±0.00)	0.00 (±0.00)	0.00 (±0.00)	0.00 (±0.00)	0.00 (±0.00)	0.00 (±0.00)
Mixed glioma	0.06 (±0.02)	0.00 (±0.01)	0.09 (±0.03)	0.14 (±0.03)	0.12 (±0.03)	0.08 (±0.03)	0.06 (±0.02)	0.17 (±0.03)	0.14 (±0.03)
Glioma malignant, NOS	0.00 (±0.01)	0.03 (±0.01)	0.11 (±0.03)	0.11 (±0.02)	0.09 (±0.02)	0.09 (±0.03)	0.13 (±0.03)	0.25 (±0.03)	0.29 (±0.04)
Choroid plexus	n<16								
Neuroepithelial	n<16								
Non–malignant and malignant neuronal/glial, neuronal and mixed	0.26 (±0.03)	0.12 (±0.03)	0.16 (±0.03)	0.07 (±0.03)	0.03 (±0.02)	0.15 (±0.03)	0.25 (±0.04)	0.28 (±0.04)	0.39 (±0.04)
Pineal parenchymal	n<16								
Embryonal/primitive/medulloblastoma	0.12 (±0.04)	0.18 (±0.04)	0.13 (±0.03)	0.16 (±0.04)	0.23 (±0.03)	0.25 (±0.04)	0.07 (±0.03)	0.20 (±0.04)	0.06 (±0.02)
TUMOURS OF CRANIAL AND SPINAL NERVES	**0.81 (±0.06)**	**1.05 (±0.07)**	**0.82 (±0.07)**	**0.91 (±0.07)**	**0.82 (±0.07)**	**0.55 (±0.07)**	**0.60 (±0.06)**	**0.62 (±0.06)**	**0.71 (±0.06)**
Schwannoma	0.81 (±0.06)	1.05 (±0.07)	0.82 (±0.07)	0.91 (±0.07)	0.82 (±0.07)	0.55 (±0.07)	0.60 (±0.06)	0.62 (±0.06)	0.71 (±0.06)
TUMOURS OF MENINGES	**3.18 (±0.11)**	**4.48 (±0.13)**	**4.10 (±0.13)**	**4.69 (±0.14)**	**4.30 (±0.13)**	**3.93 (±0.13)**	**4.75 (±0.14)**	**3.74 (±0.13)**	**3.88 (±0.13)**
Meningioma	2.94 (±0.11)	4.18 (±0.13)	4.05 (±0.12)	4.47 (±0.13)	4.22 (±0.13)	3.82 (±0.13)	4.63 (±0.13)	3.58 (±0.12)	3.75 (±0.12)
Other mesenchymal, non–malignant and malignant	n<16								
Haemangioblastoma	0.18 (±0.02)	0.21 (±0.03)	0.02 (±0.03)	0.20 (±0.03)	0.08 (±0.03)	0.03 (±0.02)	0.09 (±0.03)	0.13 (±0.03)	0.11 (±0.03)
LYMPHOMAS AND HEMOPOIETIC NEOPLASMS	n<16								
Lymphoma	n<16								
TUMOURS OF SELLAR REGION	**1.55 (±0.09)**	**1.51 (±0.09)**	**0.93 (±0.09)**	**1.83 (±0.10)**	**1.58 (±0.10)**	**1.26 (±0.08)**	**1.68 (±0.10)**	**1.25 (±0.09)**	**1.17 (±0.09)**
Pituitary	1.45 (±0.09)	1.39 (±0.09)	0.87 (±0.09)	1.59 (±0.09)	1.47 (±0.10)	1.17 (±0.08)	1.53 (±0.10)	1.05 (±0.09)	1.03 (±0.08)
Craniopharyngioma	0.09 (±0.02)	0.12 (±0.03)	0.06 (±0.02)	0.24 (±0.03)	0.11 (±0.02)	0.09 (±0.03)	0.15 (±0.03)	0.21 (±0.03)	0.14 (±0.03)
UNCLASSIFIED TUMOURS	**0.06 (±0.03)**	**0.16 (±0.03)**	**0.18 (±0.03)**	**0.08 (±0.02)**	**0.21 (±0.03)**	**0.09 (±0.03)**	**0.25 (±0.03)**	**0.11 (±0.02)**	**0.26 (±0.03)**
Haemangioma	0.06 (±0.03)	0.16 (±0.03)	0.18 (±0.03)	0.08 (±0.02)	0.21 (±0.03)	0.09 (±0.03)	0.25 (±0.03)	0.11 (±0.02)	0.26 (±0.03)
Total per Year	**9.98 (±0.24)**	**11.93 (±0.26)**	**10.93 (±0.25)**	**13.02 (±0.27)**	**11.67 (±0.26)**	**10.10 (±0.24)**	**12.74 (±0.27)**	**11.10 (±0.25)**	**11.58 (±0.25)**

6.6 *Case number tables from the current study*

TOTAL	2000	2001	2002	2003	2004	2005	2006	2007	2008	Total	% Total
TUMOURS OF NEUROEPITHELIAL TISSUE	**372.75**	**412.65**	**426.3**	**469.35**	**424.2**	**437.85**	**452.55**	**506.1**	**521.85**	**4023.6**	**52.7**
Pilocytic astrocytoma	14.7	26.25	21	32.55	19.95	10.5	19.95	16.8	22.05	183.75	**2.4**
Protoplasmic & fibrillary astrocytoma	2.1	3.15	7.35	3.15	4.2	4.2	2.1	1.05	3.15	30.45	**0.4**
Anaplastic astrocytoma	33.6	37.8	31.5	44.1	34.65	32.55	34.65	40.95	47.25	337.05	**4.4**
Unique astrocytoma variants	5.25	0	3.15	8.4	2.1	8.4	2.1	3.15	4.2	36.75	**0.5**
Astrocytoma, NOS	22.05	21	33.6	28.35	21	16.8	25.2	35.7	29.4	233.1	**3.1**
Glioblastoma	219.45	238.35	217.35	244.65	222.6	267.75	259.35	294	311.85	2275.35	**29.8**
Oligodendroglioma	11.55	23.1	34.65	31.5	38.85	18.9	25.2	23.1	11.55	218.4	**2.9**
Anaplastic oligodendroglioma	17.85	17.85	19.95	18.9	33.6	19.95	24.15	15.75	17.85	185.85	**2.4**
Ependymoma/anaplastic ependymoma	10.5	9.45	10.5	11.55	7.35	7.35	10.5	7.35	10.5	85.05	**1.1**
Ependymoma variants	0	0	0	0	0	0	0	0	0	0	**0.0**
Mixed glioma	3.15	1.05	9.45	11.55	12.6	8.4	3.15	11.55	14.7	75.6	**1.0**
Glioma malignant, NOS	1.05	1.05	9.45	7.35	4.2	9.45	9.45	15.75	16.8	74.55	**1.0**
Choroid plexus	1.05	2.1	0	2.1	3.15	1.05	1.05	0	5.25	15.75	**0.2**
Neuroepithelial	1.05	0	0	2.1	0	2.1	1.05	4.2	1.05	11.55	**0.2**
Non–malignant and malignant neuronal/glial, neuronal and mixed	12.6	11.55	13.65	8.4	4.2	14.7	15.75	18.9	18.9	118.65	**1.6**
Pineal parenchymal	0	2.1	2.1	0	3.15	0	5.25	1.05	1.05	14.7	**0.2**
Embryonal/primitive/medulloblastoma	16.8	17.85	12.6	14.7	12.6	15.75	13.65	16.8	6.3	127.05	**1.7**
TUMOURS OF CRANIAL AND SPINAL NERVES	**47.25**	**69.3**	**55.65**	**57.75**	**56.7**	**59.85**	**45.15**	**49.35**	**51.45**	**492.45**	**6.4**
Schwannoma	47.25	69.3	55.65	57.75	56.7	59.85	45.15	49.35	51.45	492.45	**6.4**
TUMOURS OF MENINGES	**151.2**	**217.35**	**207.9**	**237.3**	**232.05**	**218.4**	**257.25**	**223.65**	**233.1**	**1978.2**	**25.9**
Meningioma	141.75	200.55	195.3	219.45	222.6	211.05	244.65	210	219.45	1864.8	**24.4**
Other mesenchymal, non–malignant and malignant	2.1	4.2	2.1	4.2	1.05	4.2	2.1	1.05	2.1	23.1	**0.3**
Haemangioblastoma	7.35	12.6	10.5	13.65	8.4	3.15	10.5	12.6	11.55	90.3	**1.2**
LYMPHOMAS AND HEMOPOIETIC NEOPLASMS	**3.15**	**1.05**	**0**	**2.1**	**1.05**	**2.1**	**1.05**	**0**	**3.15**	**13.65**	**0.2**
Lymphoma	3.15	1.05	0	2.1	1.05	2.1	1.05	0	3.15	13.65	**0.2**
TUMOURS OF SELLAR REGION	**105**	**113.4**	**105**	**128.1**	**132.3**	**94.5**	**134.4**	**114.45**	**109.2**	**1036.35**	**13.6**
Pituitary	98.7	105	99.75	116.55	126	86.1	123.9	103.95	99.75	959.7	**12.6**
Craniopharyngioma	6.3	8.4	5.25	11.55	6.3	8.4	10.5	10.5	9.45	76.65	**1.0**
UNCLASSIFIED TUMOURS	**8.4**	**10.5**	**11.55**	**8.4**	**14.7**	**9.45**	**13.65**	**4.2**	**15.75**	**96.6**	**1.3**
Haemangioma	8.4	10.5	11.55	8.4	14.7	9.45	13.65	4.2	15.75	96.6	**1.3**
Total per Year	**687.75**	**824.25**	**806.4**	**903**	**861**	**822.15**	**904.05**	**897.75**	**934.5**	**7640.85**	**100.0**

MALE	2000	2001	2002	2003	2004	2005	2006	2007	2008	Total	% Total
TUMOURS OF NEUROEPITHELIAL TISSUE	**220.5**	**242.55**	**249.9**	**268.8**	**252**	**280.35**	**241.5**	**300.3**	**306.6**	**2362.5**	**62.4**
Pilocytic astrocytoma	5.25	17.85	11.55	16.8	9.45	5.25	8.4	6.3	10.5	91.35	**2.4**
Protoplasmic & fibrillary astrocytoma	2.1	1.05	4.2	1.05	3.15	2.1	0	3.15	2.1	18.9	**0.5**
Anaplastic astrocytoma	21	23.1	13.65	28.35	21	15.75	23.1	24.15	30.45	200.55	**5.3**
Unique astrocytoma variants	2.1	0	3.15	5.25	2.1	7.35	1.05	1.05	1.05	23.1	**0.6**
Astrocytoma, NOS	12.6	14.7	23.1	12.6	12.6	12.6	10.5	23.1	18.9	140.7	**3.7**
Glioblastoma	137.55	137.55	135.45	142.8	144.9	174.3	137.55	184.8	195.3	1390.2	**36.7**
Oligodendroglioma	7.35	11.55	14.7	21	19.95	15.75	10.5	16.8	5.25	122.85	**3.2**
Anaplastic oligodendroglioma	11.55	9.45	11.55	8.4	14.7	13.65	17.85	8.4	10.5	106.05	**2.8**
Ependymoma/anaplastic ependymoma	2.1	5.25	4.2	5.25	1.05	5.25	7.35	3.15	7.35	40.95	**1.1**
Ependymoma variants	0	0	0	0	0	0	0	0	0	0	**0.0**
Mixed glioma	1.05	1.05	6.3	6.3	8.4	5.25	1.05	5.25	9.45	44.1	**1.2**
Glioma malignant, NOS	1.05	0	5.25	3.15	1.05	6.3	4.2	5.25	5.25	31.5	**0.8**
Choroid plexus	0	2.1	0	1.05	3.15	0	0	0	0	6.3	**0.2**
Neuroepithelial	0	0	0	1.05	0	0	0	1.05	1.05	3.15	**0.1**
Non–malignant and malignant neuronal/glial, neuronal and mixed	4.2	7.35	8.4	6.3	3.15	9.45	7.35	8.4	4.2	58.8	**1.6**
Pineal parenchymal	0	0	0	0	2.1	0	1.05	0	1.05	4.2	**0.1**
Embryonal/primitive/medulloblastoma	12.6	11.55	8.4	9.45	5.25	7.35	11.55	9.45	4.2	79.8	**2.1**
TUMOURS OF CRANIAL AND SPINAL NERVES	**18.9**	**31.5**	**25.2**	**24.15**	**26.25**	**37.8**	**22.05**	**25.2**	**22.05**	**233.1**	**6.2**
Schwannoma	18.9	31.5	25.2	24.15	26.25	37.8	22.05	25.2	22.05	233.1	**6.2**
TUMOURS OF MENINGES	**38.85**	**54.6**	**57.75**	**61.95**	**69.3**	**68.25**	**72.45**	**75.6**	**76.65**	**575.4**	**15.2**
Meningioma	37.8	48.3	47.25	52.5	63	65.1	64.05	68.25	68.25	514.5	**13.6**
Other mesenchymal, non–malignant and malignant	0	1.05	1.05	3.15	1.05	1.05	1.05	0	1.05	9.45	**0.2**
Haemangioblastoma	1.05	5.25	9.45	6.3	5.25	2.1	7.35	7.35	7.35	51.45	**1.4**
LYMPHOMAS AND HEMOPOIETIC NEOPLASMS	**2.1**	**0**	**0**	**1.05**	**0**	**1.05**	**1.05**	**0**	**0**	**5.25**	**0.1**
Lymphoma	2.1	0	0	1.05	0	1.05	1.05	0	0	5.25	**0.1**
TUMOURS OF SELLAR REGION	**51.45**	**59.85**	**70.35**	**60.9**	**72.45**	**47.25**	**70.35**	**66.15**	**61.95**	**560.7**	**14.8**
Pituitary	48.3	55.65	67.2	57.75	70.35	42	65.1	63	57.75	527.1	**13.9**
Craniopharyngioma	3.15	4.2	3.15	3.15	2.1	5.25	5.25	3.15	4.2	33.6	**0.9**
UNCLASSIFIED TUMOURS	**6.3**	**5.25**	**5.25**	**5.25**	**7.35**	**6.3**	**4.2**	**0**	**6.3**	**46.2**	**1.2**
Haemangioma	6.3	5.25	5.25	5.25	7.35	6.3	4.2	0	6.3	46.2	**1.2**
Total per Year	**338.1**	**393.75**	**408.45**	**422.1**	**427.35**	**441**	**411.6**	**467.25**	**473.55**	**3783.15**	**100.0**

FEMALE	2000	2001	2002	2003	2004	2005	2006	2007	2008	Total	% Total
TUMOURS OF NEUROEPITHELIAL TISSUE	**152.25**	**170.1**	**176.4**	**200.55**	**172.2**	**157.5**	**211.05**	**208.95**	**216.3**	**1665.3**	**43.1**
Pilocytic astrocytoma	9.45	8.4	9.45	15.75	10.5	5.25	11.55	10.5	11.55	92.4	**2.4**
Protoplasmic & fibrillary astrocytoma	0	2.1	3.15	2.1	1.05	2.1	2.1	1.05	2.1	15.75	**0.4**
Anaplastic astrocytoma	12.6	14.7	17.85	15.75	13.65	16.8	11.55	16.8	16.8	136.5	**3.5**
Unique astrocytoma variants	3.15	0	0	3.15	0	1.05	1.05	2.1	3.15	13.65	**0.4**
Astrocytoma, NOS	9.45	6.3	10.5	15.75	8.4	4.2	14.7	12.6	10.5	92.4	**2.4**
Glioblastoma	81.9	100.8	81.9	101.85	77.7	93.45	121.8	109.2	116.55	885.15	**22.9**
Oligodendroglioma	4.2	11.55	19.95	10.5	18.9	3.15	14.7	6.3	6.3	95.55	**2.5**
Anaplastic oligodendroglioma	6.3	8.4	8.4	10.5	18.9	6.3	6.3	7.35	7.35	79.8	**2.1**
Ependymoma/anaplastic ependymoma	8.4	4.2	6.3	6.3	6.3	2.1	3.15	4.2	3.15	44.1	**1.1**
Ependymoma variants	0	0	0	0	0	0	0	0	0	0	**0.0**
Mixed glioma	2.1	0	3.15	5.25	4.2	3.15	2.1	6.3	5.25	31.5	**0.8**
Glioma malignant, NOS	0	1.05	4.2	4.2	3.15	3.15	5.25	10.5	11.55	43.05	**1.1**
Choroid plexus	1.05	0	0	1.05	0	1.05	1.05	0	5.25	9.45	**0.2**
Neuroepithelial	1.05	0	0	1.05	0	2.1	1.05	3.15	0	8.4	**0.2**
Non–malignant and malignant neuronal/glial, neuronal and mixed	8.4	4.2	5.25	2.1	1.05	5.25	8.4	10.5	14.7	59.85	**1.5**
Pineal parenchymal	0	2.1	2.1	0	1.05	0	4.2	1.05	0	10.5	**0.3**
Embryonal/primitive/medulloblastoma	4.2	6.3	4.2	5.25	7.35	8.4	2.1	7.35	2.1	47.25	**1.2**
TUMOURS OF CRANIAL AND SPINAL NERVES	**28.35**	**37.8**	**30.45**	**33.6**	**30.45**	**22.05**	**23.1**	**24.15**	**29.4**	**259.35**	**6.7**
Schwannoma	28.35	37.8	30.45	33.6	30.45	22.05	23.1	24.15	29.4	259.35	**6.7**
TUMOURS OF MENINGES	**112.35**	**162.75**	**150.15**	**175.35**	**162.75**	**150.15**	**184.8**	**148.05**	**156.45**	**1402.8**	**36.3**
Meningioma	103.95	152.25	148.05	166.95	159.6	145.95	180.6	141.75	151.2	1350.3	**35.0**
Other mesenchymal, non–malignant and malignant	2.1	3.15	1.05	1.05	0	3.15	1.05	1.05	1.05	13.65	**0.4**
Haemangioblastoma	6.3	7.35	1.05	7.35	3.15	1.05	3.15	5.25	4.2	38.85	**1.0**
LYMPHOMAS AND HEMOPOIETIC NEOPLASMS	**1.05**	**1.05**	**0**	**1.05**	**1.05**	**1.05**	**0**	**0**	**3.15**	**8.4**	**0.2**
Lymphoma	1.05	1.05	0	1.05	1.05	1.05	0	0	3.15	8.4	**0.2**
TUMOURS OF SELLAR REGION	**53.55**	**53.55**	**34.65**	**67.2**	**59.85**	**47.25**	**64.05**	**48.3**	**47.25**	**475.65**	**12.3**
Pituitary	50.4	49.35	32.55	58.8	55.65	44.1	58.8	40.95	42	432.6	**11.2**
Craniopharyngioma	3.15	4.2	2.1	8.4	4.2	3.15	5.25	7.35	5.25	43.05	**1.1**
UNCLASSIFIED TUMOURS	**2.1**	**5.25**	**6.3**	**3.15**	**7.35**	**3.15**	**9.45**	**4.2**	**9.45**	**50.4**	**1.3**
Haemangioma	2.1	5.25	6.3	3.15	7.35	3.15	9.45	4.2	9.45	50.4	**1.3**
Total per Year	**349.65**	**430.5**	**397.95**	**480.9**	**433.65**	**381.15**	**492.45**	**433.65**	**462**	**3861.9**	**100.0**

6.7 Histological Subtype Graphs – Incidence by Age Groupings

Only tumours with number >300 over the years 2000-2008 are included in the figures below.

An example of crunching numbers until significance is found. All male benign tumours are analysed in **Figure 6.2** below using one joinpoint and exponential regression analysis assuming a Poisson distribution. When no joinpoints are used, no significant trend is identified, but given the low data point in the year 2000, analysis with an additional joinpoint given two significant trends. This type of analysis was avoided and the current analysis concentrated only on major histological subgroups to reduce the amount of erroneous conclusion through small sample size.

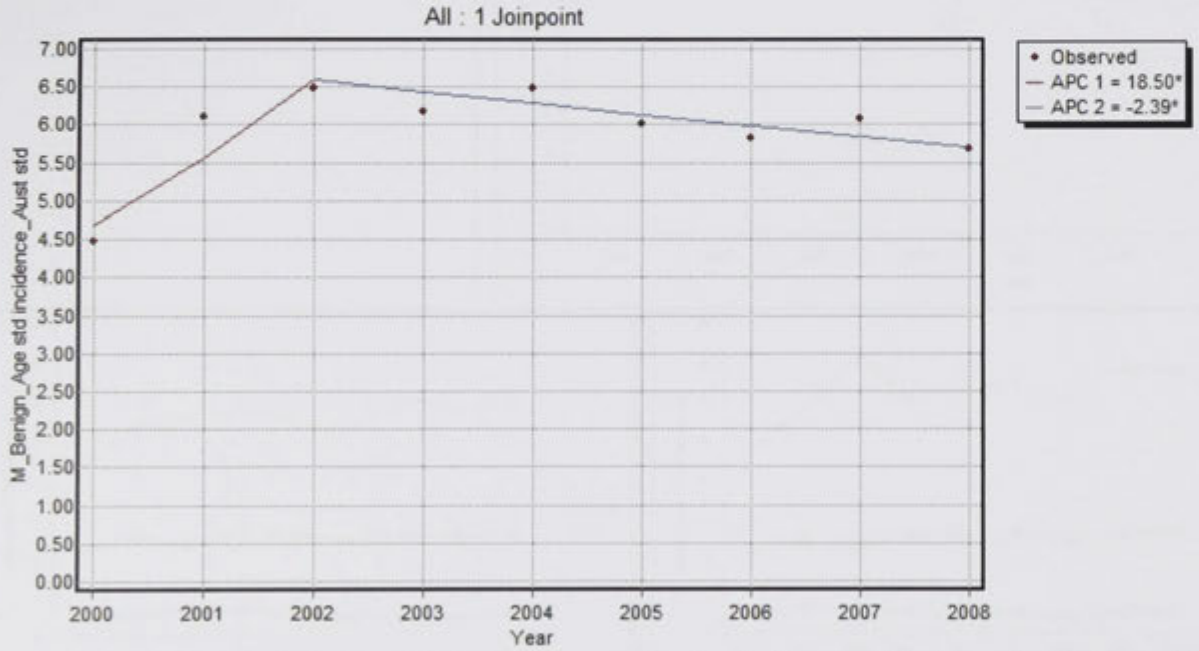
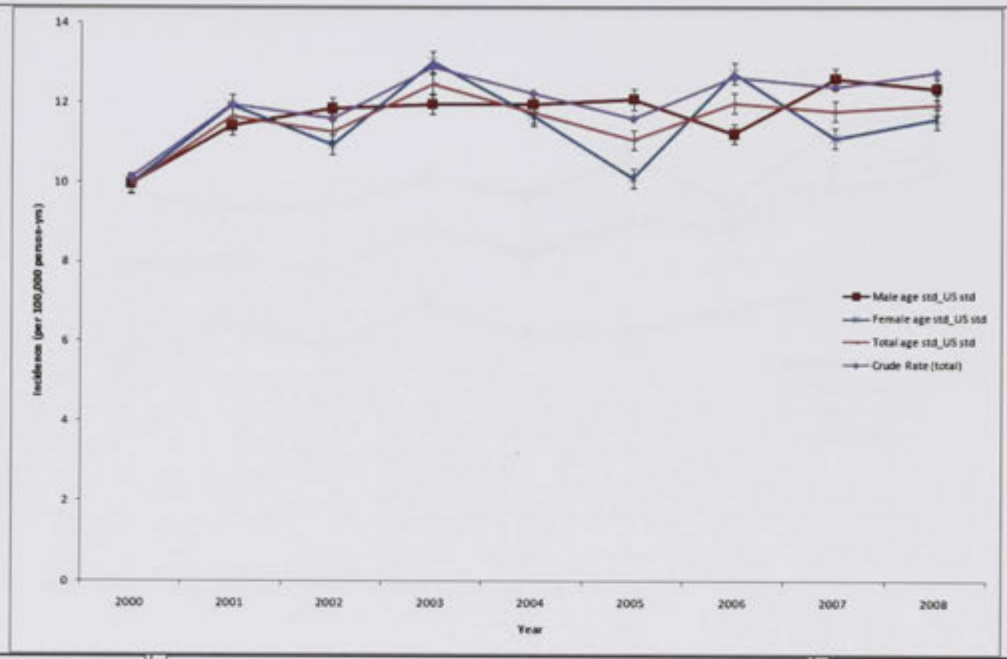


Figure 6.2. Joinpoint analysis of all male benign brain tumours showing significant trends when analysed using one joinpoint. When no joinpoint is used, the trend demonstrates no significant trend up or down, highlighting the issue of significance hunting.

6.7.1 All tumours

General

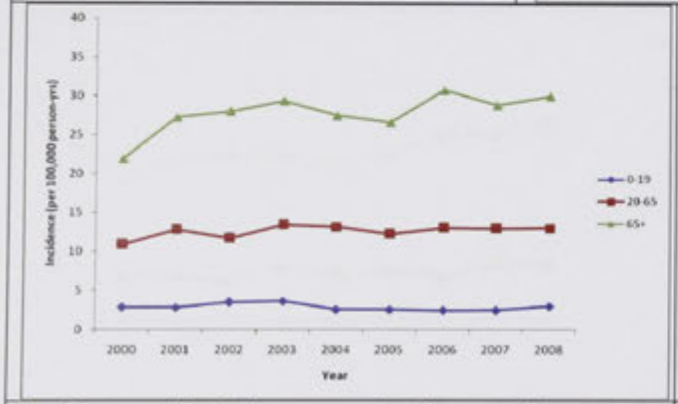
Age-standardised incidence rates for all tumours by gender over the years 2000-2008. 95% confidence intervals are displayed. Rates are standardised to the 2000 US Standard Population.



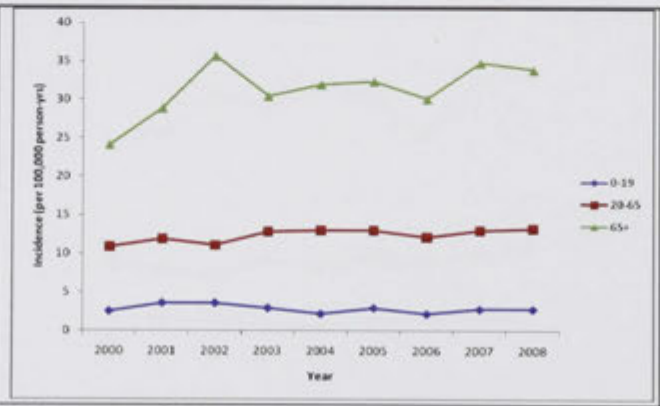
Joinpoint Regression Analysis

Subgroup		APC (%)	95% CI for APCs
Total		**1.2**	**-0.6, 3.0**
	0-19	-	-
	20-64	-	-
	65+	0.7	-1.6, 2.9
Male		**1.7***	**0.1, 3.3**
	0-19	-	-
	20-64	-	-
	65+	-	-
Female		**0.7**	**-2.3, 3.7**
	0-19	-	-
	20-64	-	-
	65+	-	-

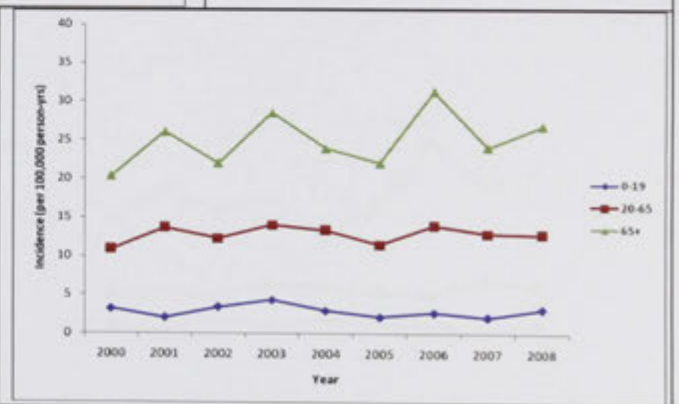
*denotes significance. APC is statistically significant from zero. All models are Poisson regression. APC, annual percentage change; CI, confidence intervals.



Total age-specific incidence rates for all tumours by age group



Male age-specific incidence rates for all tumours by age group

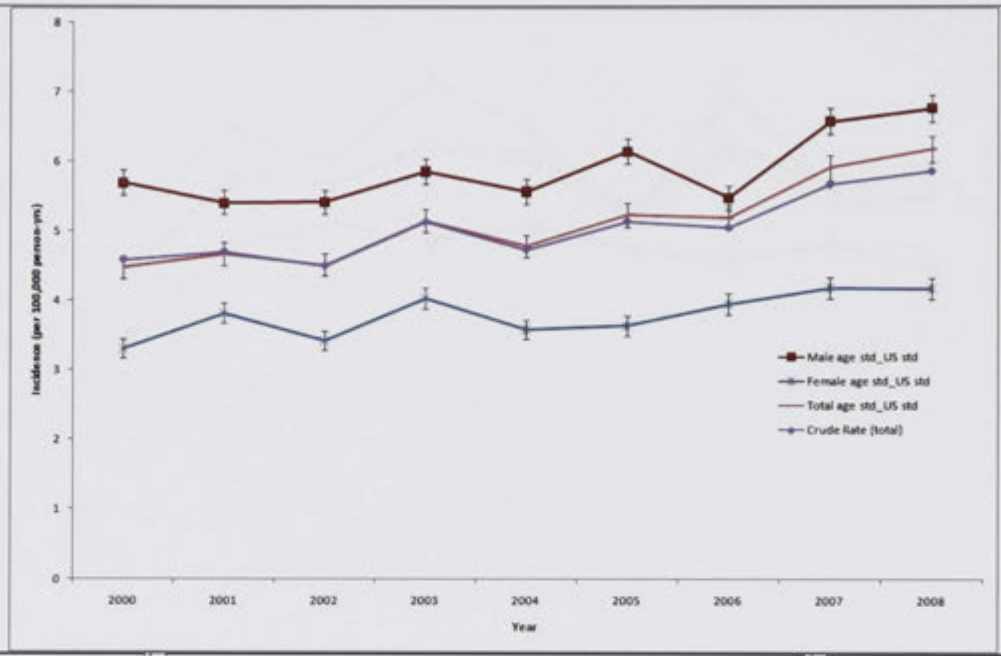


Female age-specific incidence rates for all tumours by age group

6.7.2 Malignant Tumours

General

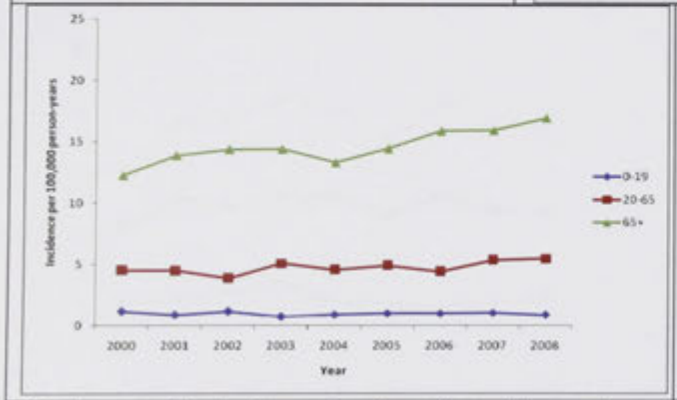
Age-standardised incidence rates for malignant tumours by gender over the years 2000-2008. 95% confidence intervals are displayed. Rates are standardised to the 2000 US Standard Population.



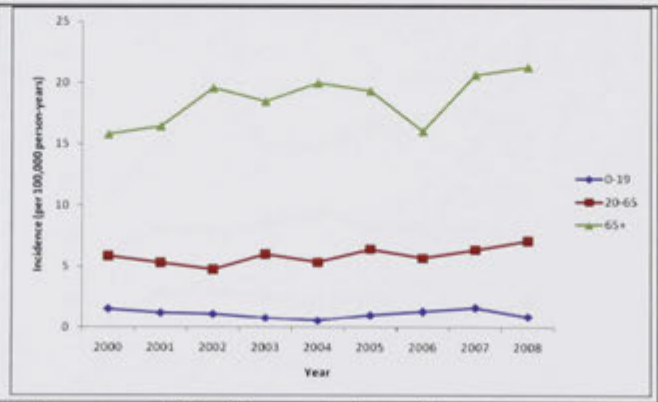
Joinpoint Regression Analysis

Subgroup		APC (%)	95% CI for APCs
Total		**3.9***	**2.4, 5.4**
	0-19	-	-
	20-64	-	-
	65+	1.5*	0.1, 3.0
Male		**2.3***	**0.4, 4.2**
	0-19	-	-
	20-64	-	-
	65+	0.6	-2.1, 3.4
Female		**2.3***	**0.3, 4.3**
	0-19	-	-
	20-64	-	-
	65+	2.6	-2.7, 8.2

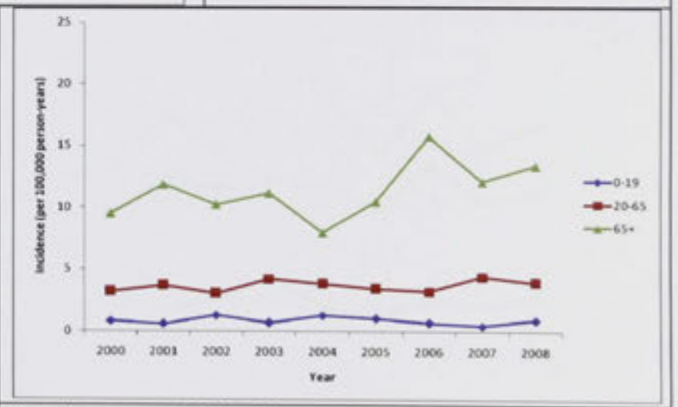
*denotes significance. APC is statistically significant from zero. All models are Poisson regression. APC, annual percentage change; CI, confidence intervals.



Total age-specific incidence rates for malignant tumours by age group



Male age-specific incidence rates for malignant tumours by age group

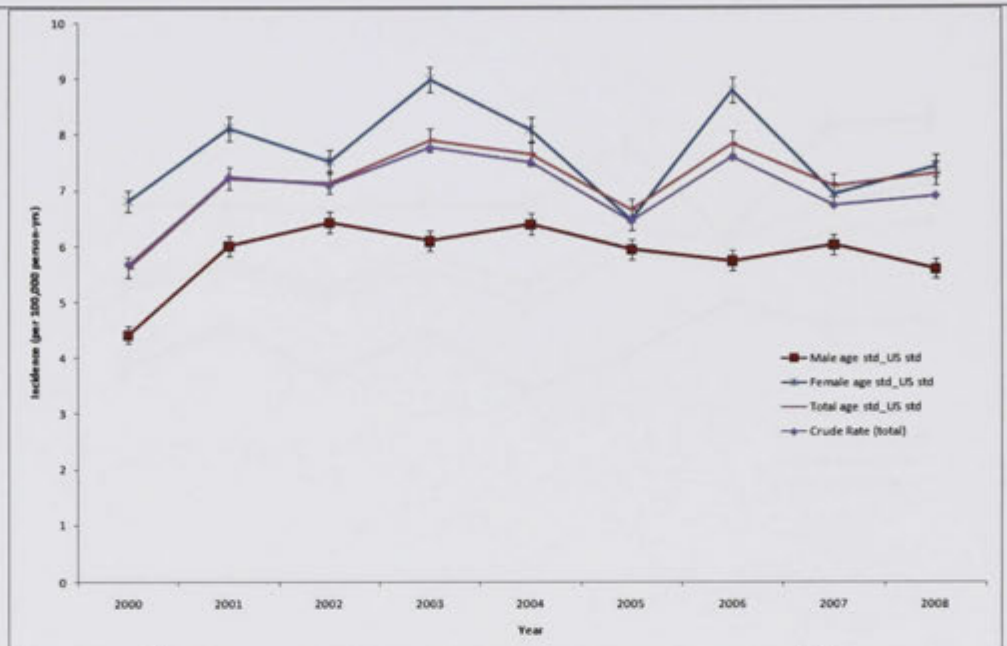


Female age-specific incidence rates for malignant tumours by age group

6.7.3 Benign Tumours

General

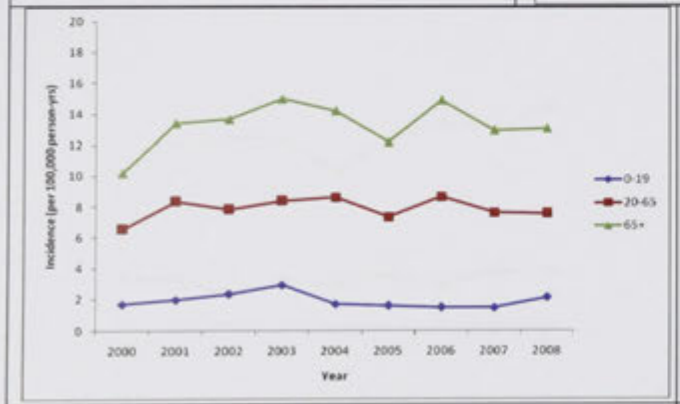
Age-standardised incidence rates for benign tumours by gender over the years 2000-2008. 95% confidence intervals are displayed. Rates are standardised to the 2000 US Standard Population.



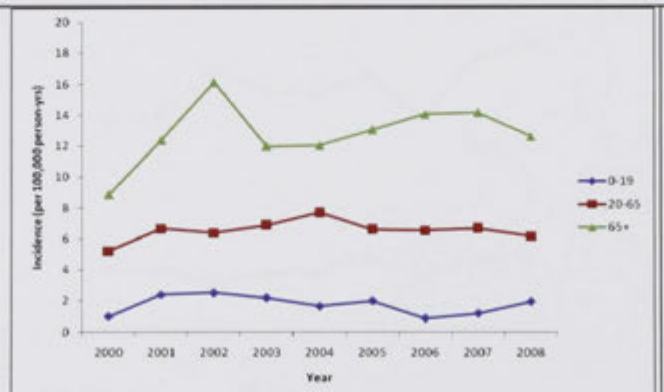
Joinpoint Regression Analysis

Subgroup	APC (%)	95% CI for APCs
Total	**1.7**	**-1.4, 4.9**
0-19	-	-
20-64	-	-
65+	-	-
Male	**1.1**	**-2.3, 4.7**
0-19	-	-
20-64	-	-
65+	-	-
Female	**-0.2**	**-3.9, 3.6**
0-19	-	-
20-64	-	-
65+	-	-

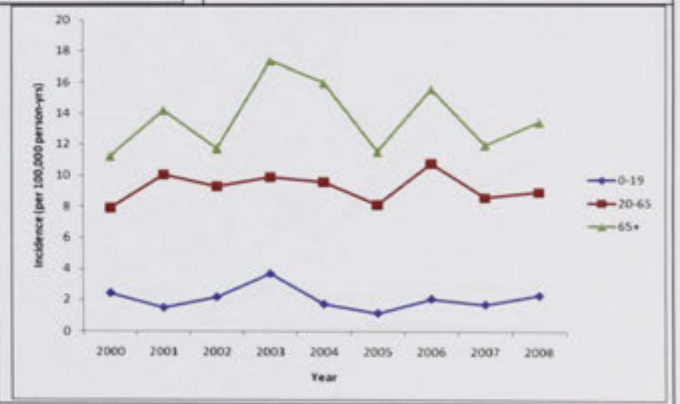
*denotes significance. APC is statistically significant from zero. All models are Poisson regression. APC, annual percentage change; CI, confidence intervals.



Total age-specific incidence rates for benign tumours by age group



Male age-specific incidence rates for benign tumours by age group



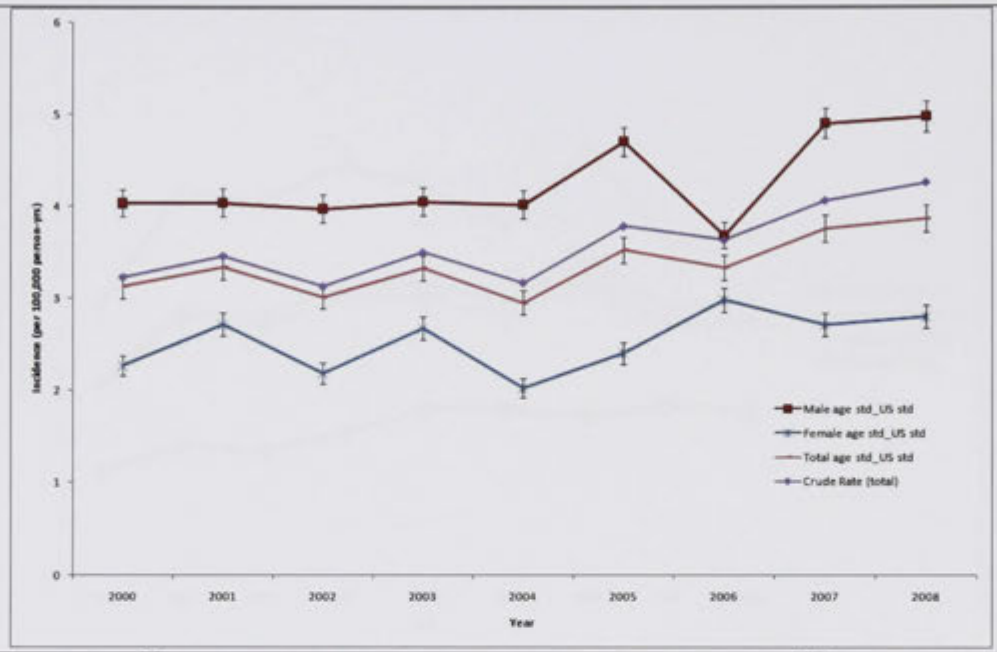
Female age-specific incidence rates for benign tumours by age group

6.7.4 Glioblastoma

General

Glioblastoma includes all cases of glioblastoma multiforme, gliosarcoma, and giant cell glioblastoma (codes M 9440 M 9441 M 9442).

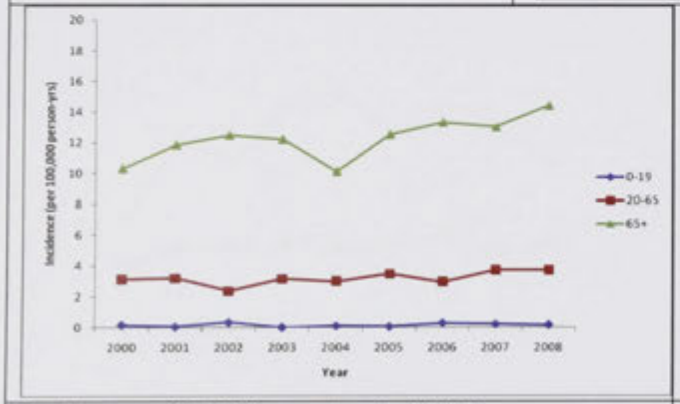
Age-standardised incidence rates for GBM by gender over the years 2000-2008. 95% confidence intervals are displayed. Rates are standardised to the 2000 US Standard Population.



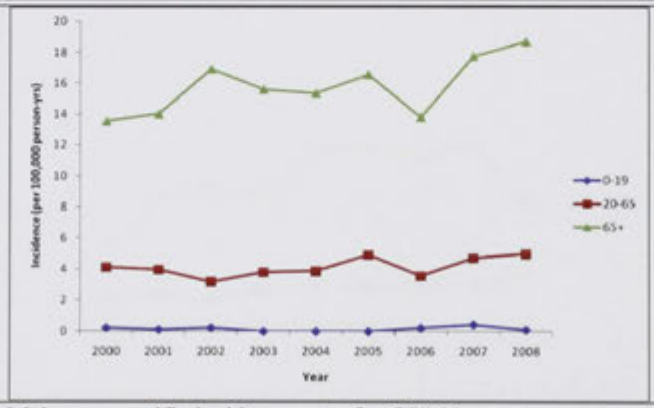
Joinpoint Regression Analysis

Subgroup		APC (%)	95% CI for APCs
Total		**2.5***	**0.4, 4.6**
	0-19	-	-
	20-64	2.8	-0.7, 6.4
	65+	3.0*	0.5, 5.6
Male		**2.6**	**-0.1, 5.4**
	0-19	-	-
	20-64	3.1	-0.9, 7.3
	65+	2.9*	0.1, 5.8
Female		**2.2**	**-1.5, 6.0**
	0-19	-	-
	20-64	2.2	-2.2, 6.8
	65+	3.2	-2.9, 9.6

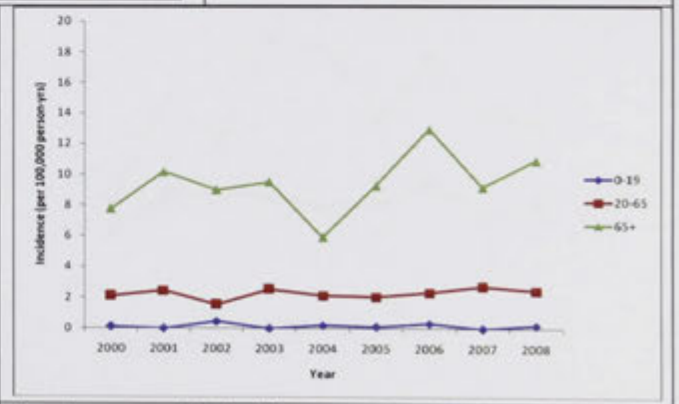
*denotes significance. APC is statistically significant from zero. All models are Poisson regression. APC, annual percentage change; CI, confidence intervals.



Total age-specific incidence rates for GBM by age group



Male age-specific incidence rates for GBM by age group

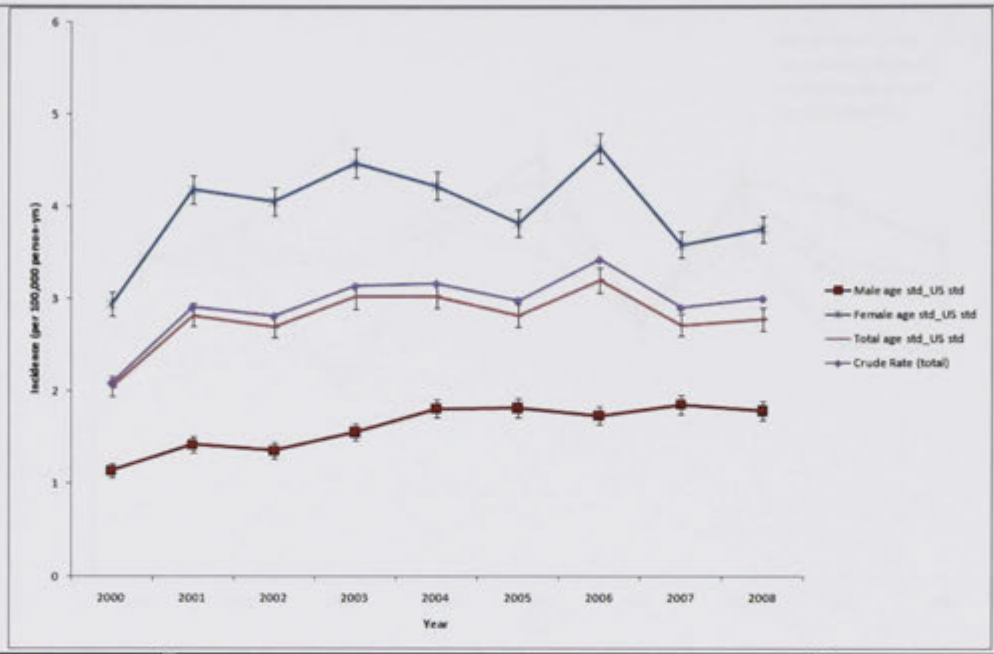


Female age-specific incidence rates for GBM by age group

6.7.5 Meningioma

General

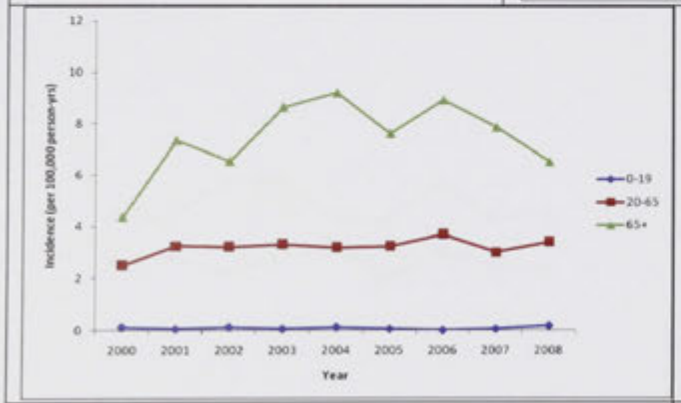
Age-standardised incidence rates for meningioma by gender over the years 2000-2008. 95% confidence intervals are displayed. Rates are standardised to the 2000 US Standard Population.



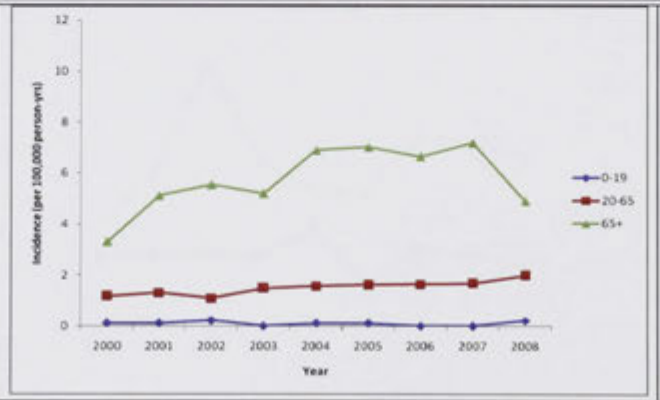
Joinpoint Regression Analysis

Subgroup		APC (%)	95% CI for APCs
Total		**1.9**	**-1.6, 5.5**
	0-19	-	-
	20-64	1.9	-0.9, 4.9
	65+	2.9	-3.6, 9.8
Male		**5.3***	**2.6, 8.1**
	0-19	-	-
	20-64	6.3*	3.8, 8.8
	65+	5.0	-1.4, 12.0
Female		**0.6**	**-3.6, 5.0**
	0-19	-	-
	20-64	0.5	-3.2, 4.4
	65+	1.9	-5.8, 10.1

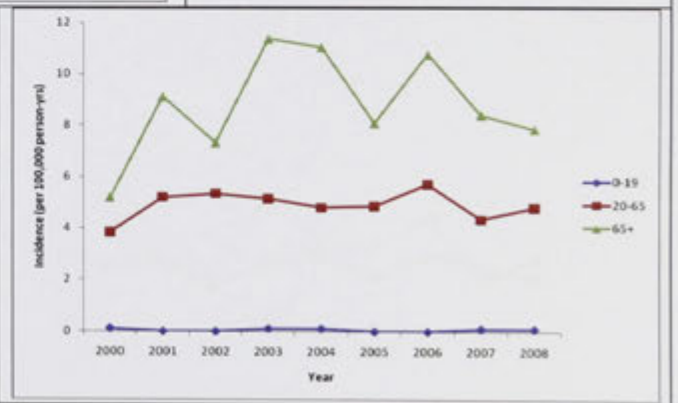
*denotes significance. APC is statistically significant from zero. All models are Poisson regression. APC, annual percentage change; CI, confidence intervals.



Total age-specific incidence rates for meningioma by age group



Male age-specific incidence rates for meningioma by age group

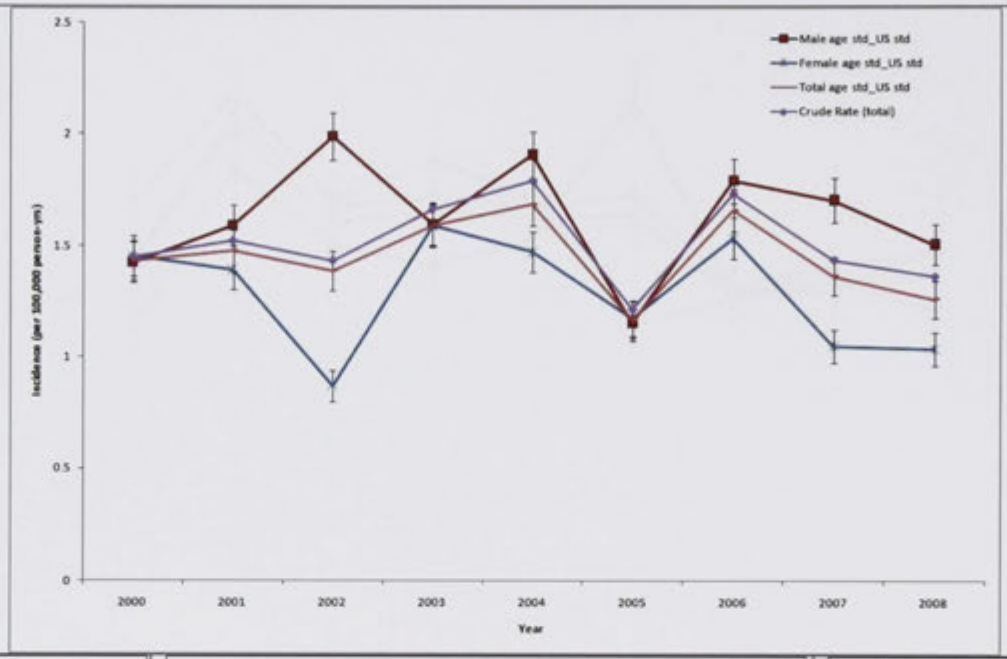


Female age-specific incidence rates for meningioma by age group

6.7.6 Pituitary Adenoma

General

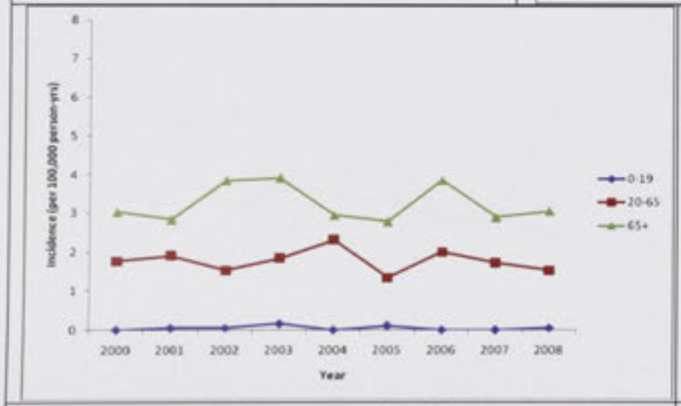
Age-standardised incidence rates for pituitary adenoma by gender over the years 2000-2008. 95% confidence intervals are displayed. Rates are standardised to the 2000 US Standard Population.



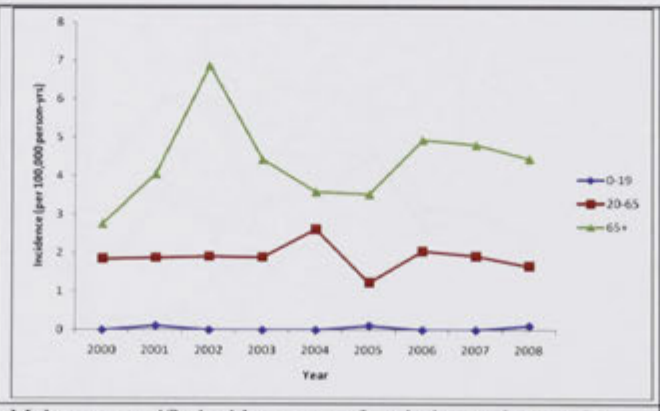
Joinpoint Regression Analysis

Subgroup		APC (%)	95% CI for APCs
Total		**-1.0**	**-5.1, 3.2**
	0-19	-	-
	20-64	-0.8	-6.1, 4.7
	65+	-0.8	-5.5, 4.2
Male		**-0.5**	**-5.5, 4.8**
	0-19	-	-
	20-64	-0.9	-7.1, 5.7
	65+	0.4	-0.8, 9.6
Female		**-2.1**	**-8.3, 4.5**
	0-19	-	-
	20-64	-0.9	-6.7, 5.3
	65+	-4.2	-13.3, 5.9

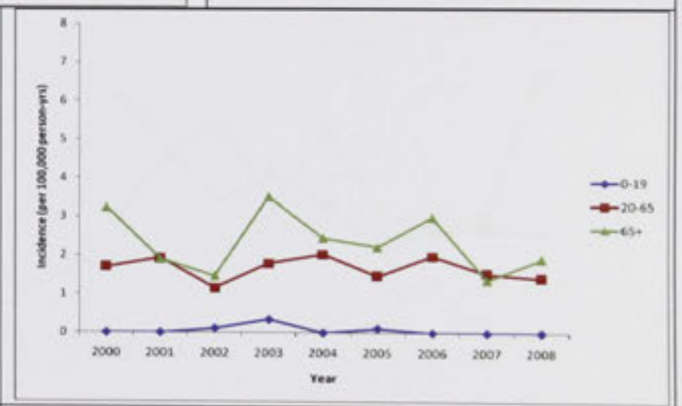
*denotes significance. APC is statistically significant from zero. All models are Poisson regression. APC, annual percentage change; CI, confidence intervals.



Total age-specific incidence rates for pituitary adenoma by age group



Male age-specific incidence rates for pituitary adenoma by age group

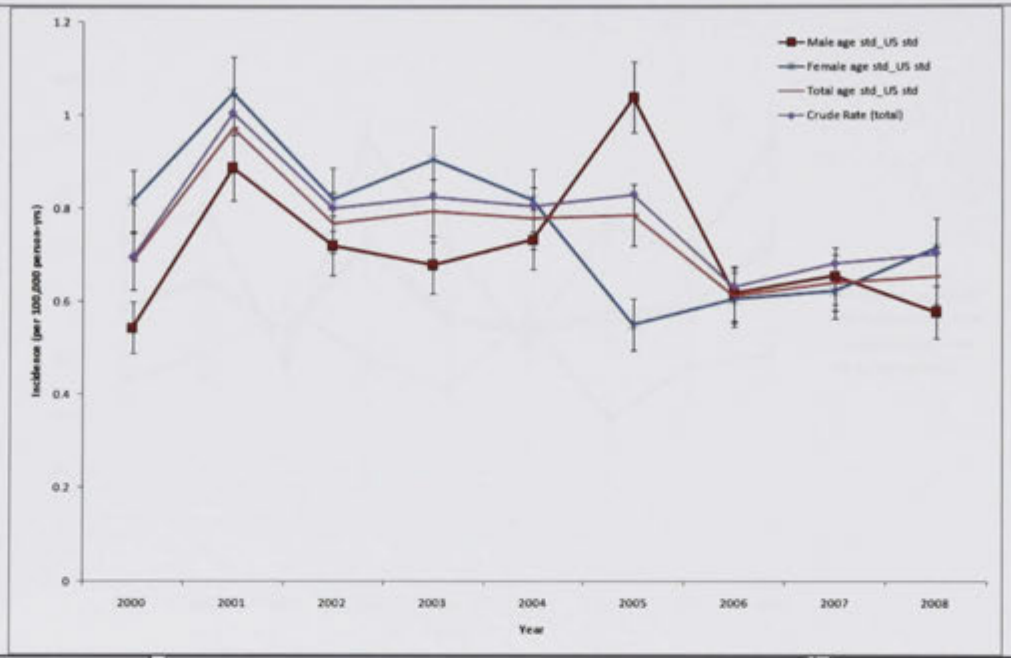


Female age-specific incidence rates for pituitary adenoma by age group

6.7.7 Schwannoma

General

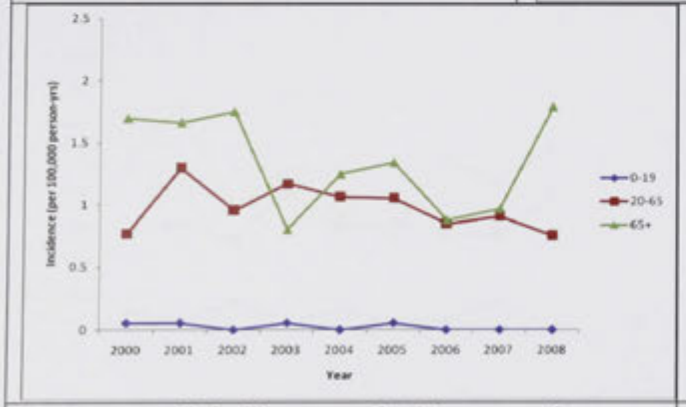
Age-standardised incidence rates for Schwannoma by gender over the years 2000-2008. 95% confidence intervals are displayed. Rates are standardised to the 2000 US Standard Population.



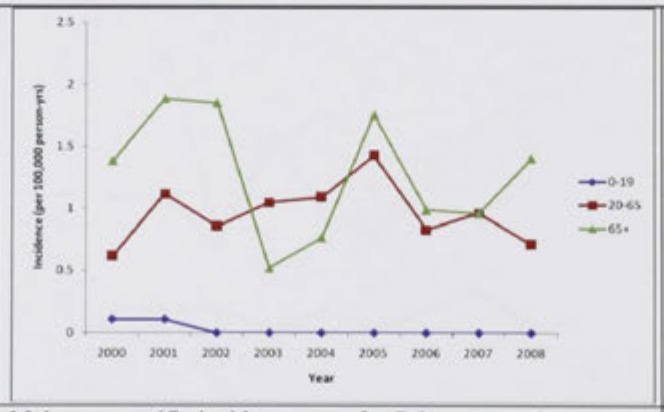
Joinpoint Regression Analysis

Subgroup		APC (%)	95% CI for APCs
Total		**-3.5**	**-7.2, 0.5**
	0-19	-	-
	20-64	-3.0	-8.4, 2.6
	65+	-2.9	-10.7, 5.7
Male		**-1.0**	**-7.9, 6.3**
	0-19	-	-
	20-64	0.3	-8.1, 9.6
	65+	-4.2	-14.3, 7.1
Female		**-5.3***	**-9.9, -0.5**
	0-19	-	-
	20-64	-5.8	-11.6, 0.3
	65+	-1.8	-10.9, 8.3

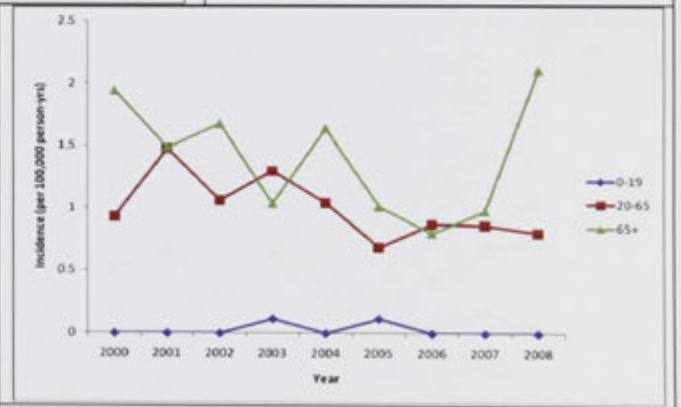
*denotes significance. APC is statistically significant from zero. All models are Poisson regression. APC, annual percentage change; CI, confidence intervals.



Total age-specific incidence rates for Schwannoma by age group



Male age-specific incidence rates for Schwannoma by age group

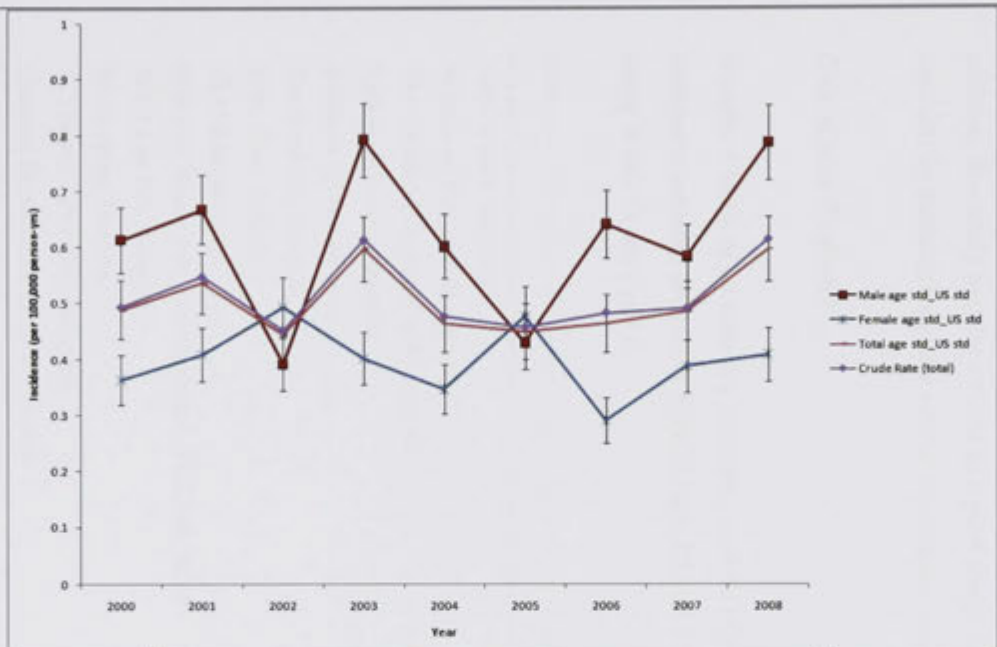


Female age-specific incidence rates for Schwannoma by age group

6.7.8 Anaplastic Astrocytoma

General

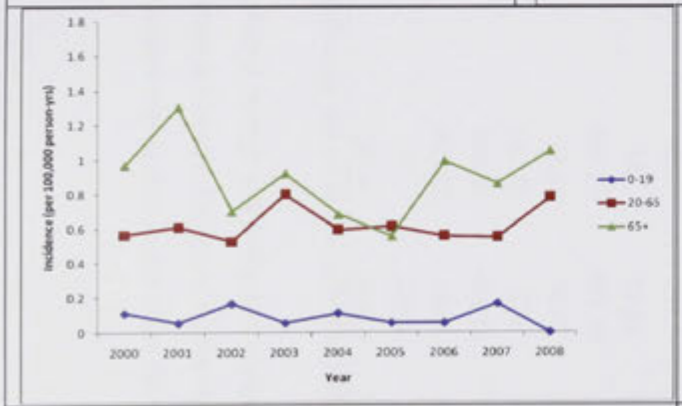
Age-standardised incidence rates for anaplastic astrocytoma by gender over the years 2000-2008. 95% confidence intervals are displayed. Rates are standardised to the 2000 US Standard Population.



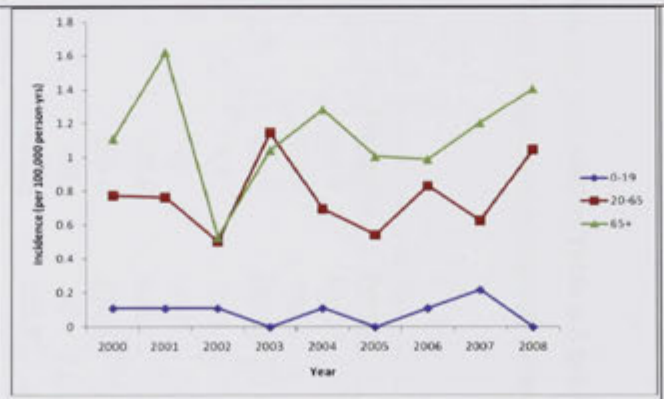
Joinpoint Regression Analysis

Subgroup	APC (%)	95% CI for APCs
Total	**0.7**	**-3.1, 4.5**
0-19	-	-
20-64	-	-
65+	-	-
Male	**1.5**	**-5.3, 8.8**
0-19	-	-
20-64	-	-
65+	-	-
Female	**-0.8**	**-5.5, 4.3**
0-19	-	-
20-64	-	-
65+	-	-

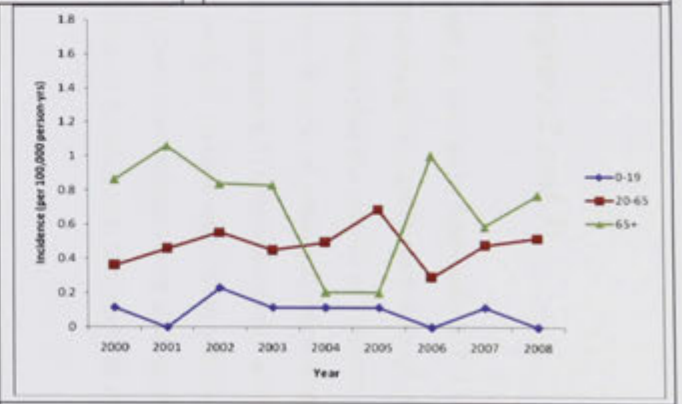
*denotes significance. APC is statistically significant from zero. All models are Poisson regression. APC, annual percentage change; CI, confidence intervals.



Total age-specific incidence rates for anaplstic astrocytoma by age group



Male age-specific incidence rates for anaplstic astrocytoma by age group



Female age-specific incidence rates for anaplstic astrocytoma by age group

6.8 Additional Results (not included in Chapters 2 and 3)

Results not presented in the papers above are offered here as well as in **Appendix 6.7**. I have included these results for completeness but continual searching for significance through subtype analysis was not extensively performed. The reason for this is that the chance of random significance increases with continual analysis, particularly in view of small numbers inherent to brain tumour data. An example was provided above (**Appendix 6.7**) where Joinpoint analysis of benign tumours in males only using multiple points of analysis yielded significant trends. In addition, this study may be viewed as a pilot study, and given the limitations on data quality imposed by methodology and ethical constraints; significance hunting was treated with caution.

Descriptive Statistics

Weighted totals of all tumours according to WHO Grade are presented in **Table 6.8** below, with malignant tumours defined as WHO Grade III and IV, and benign (non-malignant) tumours being WHO Grade I and II.

	Malignant	Benign	Total
John Hunter Hospital	300.3	406.35	706.65
Westmead Pub_Priv Hospitals	329.7	254.1	583.8
The Children's Hospital at Westmead	49.35	127.05	176.4
Sydney Adventist Hospital	2.1	3.15	5.25
Dalcross Private Hospital	0	1.05	1.05
The Canberra Hospital	205.8	262.5	468.3
RNS, Dalx & NSP	653.1	623.7	1276.8
The Mater Hospital	1.05	0	1.05
Prince of Wales Pub_Priv Hospitals_STG Pub_SCH	624.75	510.3	1135.05
St George Priv Hospital	92.4	157.5	249.9
Wollongong Hospital	84	85.05	169.05
St Vincent's Pub_Priv Hospitals	202.65	658.35	861
Concord Repatriation General Hospital	75.6	76.65	152.25
Liverpool Hospital	112.35	273	385.35
Royal Prince Alfred Hospital	364.35	662.55	1026.9
Nepean Hospital	103.95	132.3	236.25
POW Cancer Centre	0	205.8	205.8
Total	3201.45	4439.4	7640.85

Table 6.8. Weighted totals of tumours sourced from each pathology collection site by WHO Grade.

Figures 6.3, 6.4 and 6.5 demonstrate the proportion of total, benign and malignant tumours received from each participating centre. Data were complete from the Prince of Wales Hospital (POW) site only from mid-1999, and hence our full analysis was limited to the years 2000-

2008, despite other centres having more complete data prior to this date. It was thought that analysis without the POW data prior to the year 2000 would introduce an insurmountable degree of sampling error.

The largest load of tumours was sourced from the databases at Royal North Shore Hospital (17%), Prince of Wales Hospital (15%) and Royal Prince Alfred Hospital (13%) (which in fact includes Liverpool (5%) and Concord Repatriation General (2%) Hospitals pathological data) (**Figure 6.3**).

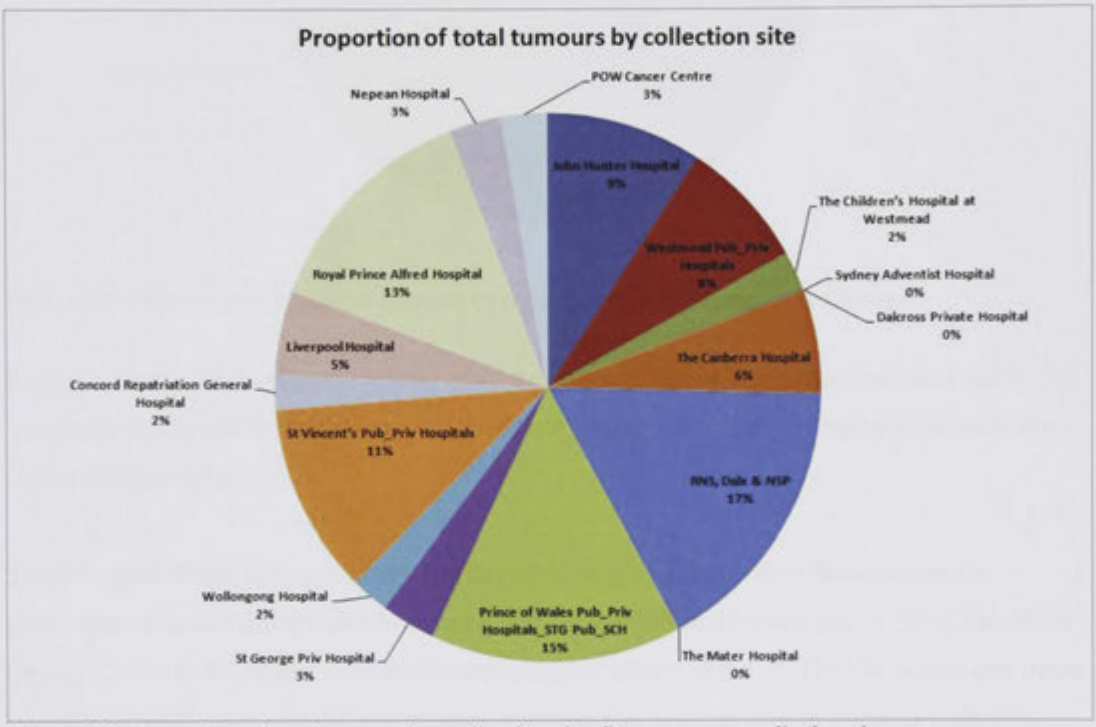


Figure 6.3. Proportion of total tumours by collection site. Percentages are displayed. Abbreviations: POW – Prince of Wales, Pub – public, Priv – private, STG – St George Hospital, SCH – Sydney Childrens Hospital, RNS – Royal North Shore, Dalx – Dalcross Private Hospital, NSP – North Shore Private Hospital.

The majority of malignant tumours were also collected from the three centres named above with approximately 60% of all malignant tumours in the study originating from these sources in relatively equal proportions (**Figure 6.4**).

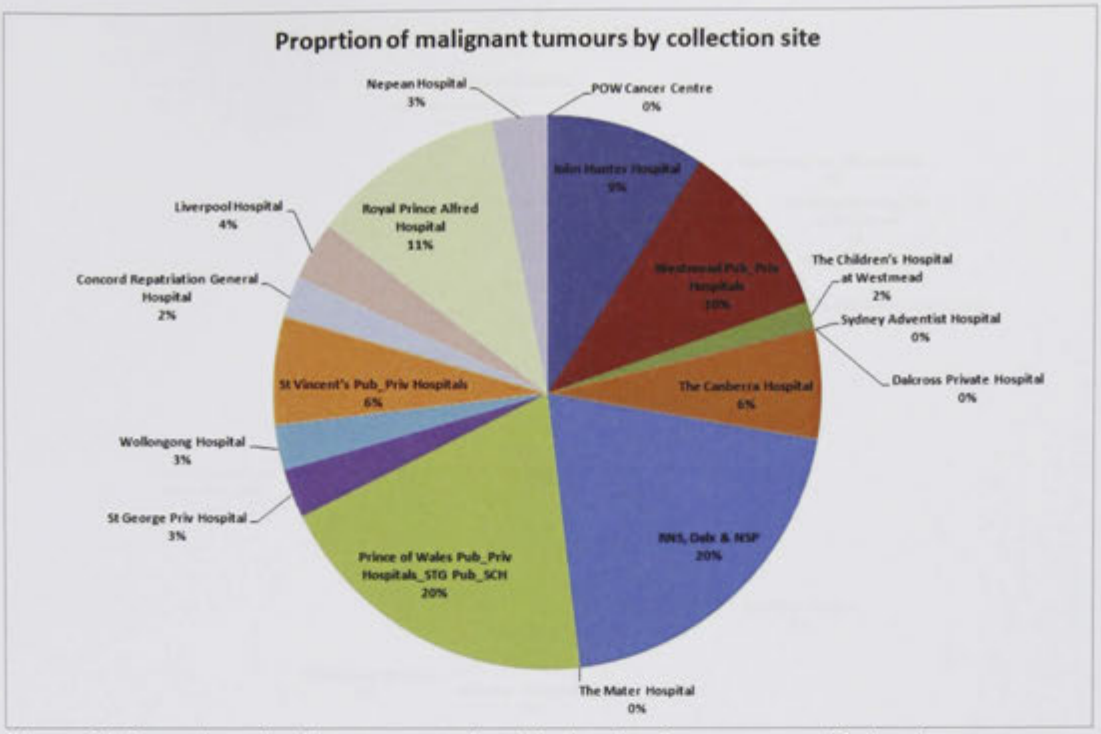


Figure 6.4. Proportion of malignant tumours by collection site. Percentages are displayed.

Benign tumours were collected mostly from the Royal Prince Alfred collection site (~23%), St Vincent's Public and Private Hospitals (15%) and Royal North Shore Hospital collection site (14%) (**Figure 6.5**).

The Prince of Wales Cancer Centre data has also been included here to demonstrate the proportion of non-histologically confirmed tumours contributed by this centre (5%). The POW Cancer Centre is the largest stereotactic radiosurgical centre in the ACT/NSW region and treats tumours generally not amenable to surgical excision due to either size or location within the brain. Analysis of this data is referred to only passingly in the current study but included for completeness.

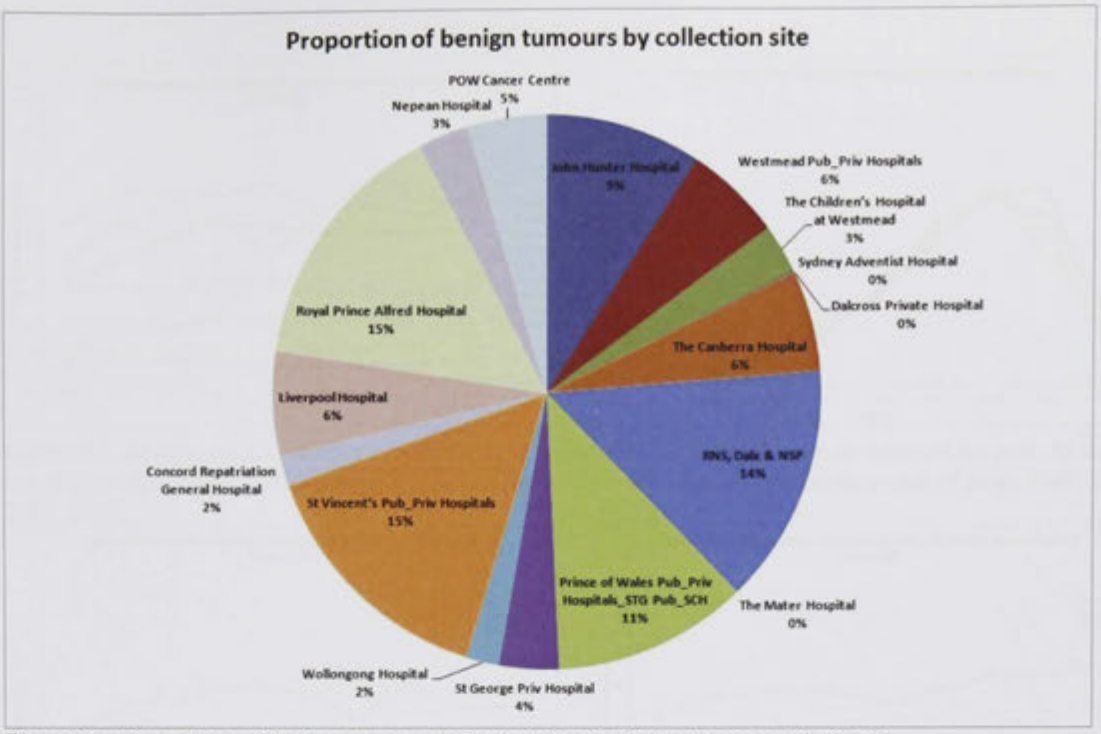
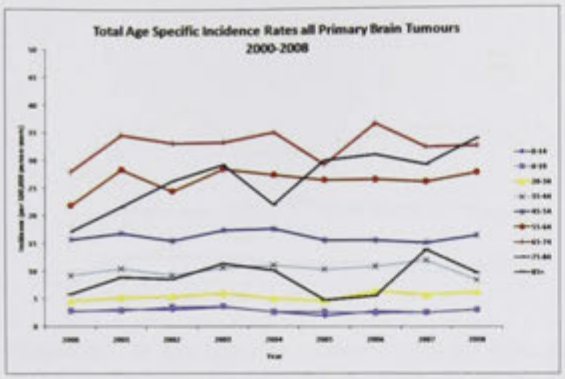


Figure 6.5. Proportion of benign tumours by collection site. Percentages are displayed.

Figures 6.6, 6.7 and 6.8 present US-standardised incidence rates for all primary brain tumours by 10 year age groups and gender in the period 2000 – 2008 as well as comparison between earlier (2000, 2001) and later (2007, 2008) years of study. Peak incidence is found in older patients (aged 65 – 74 years) with average incidence rates of 32.72 (total), 34.08 (male), 31.45 (female) cases per 100,000 person-years across the years of study. Slightly higher incidence rates are seen in later years of study in patients aged 75-84 years for total population (**Figure 6.6b**)).



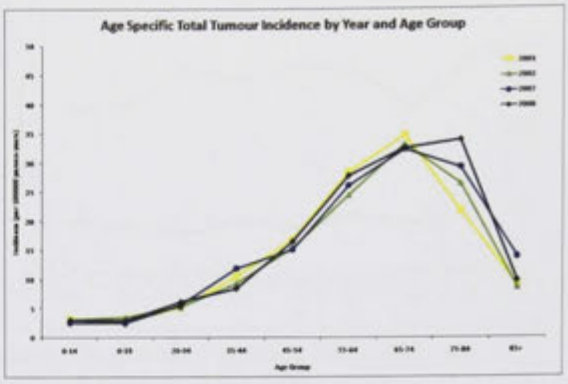
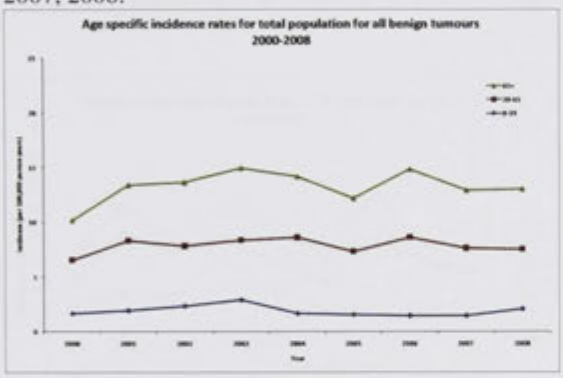


Figure 6.6. a) Age specific incidence rates for total population for all primary brain tumours by year. **b)** Age specific incidence rates for total population for all primary brain tumours with comparison of years 2001, 2002, 2007, 2008.



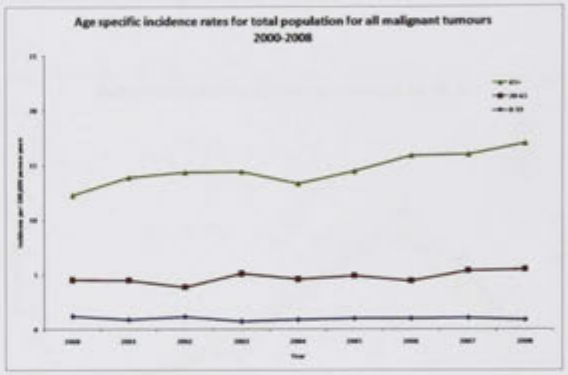
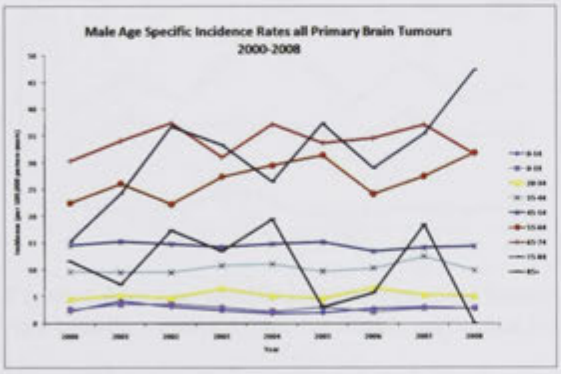


Figure 6.6. c) Age specific incidence rates for total population for all benign tumours, 2000-2008. **d)** Age specific incidence rates for total population for all malignant tumours, 2000-2008.

Male incidence rates are slightly higher than female incidence rates in the older populations, particularly persons aged 74 – 84 years.



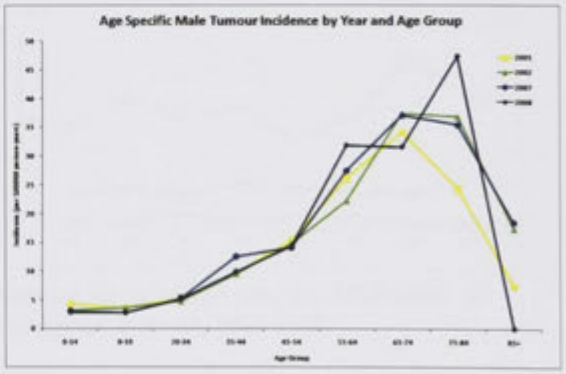
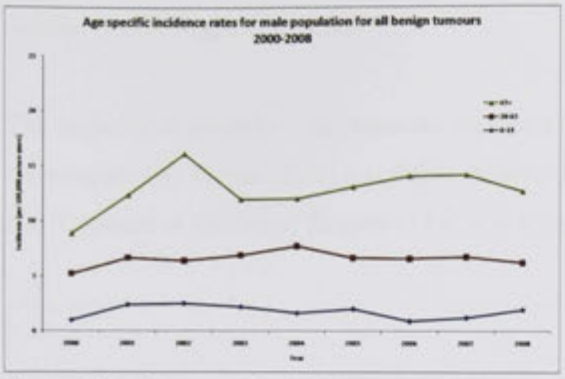


Figure 6.7. a) Age specific incidence rates for male population for all primary brain tumours by year. **b)** Age specific incidence rates for male population for all primary brain tumours with comparison of years 2001, 2002, 2007, 2008.



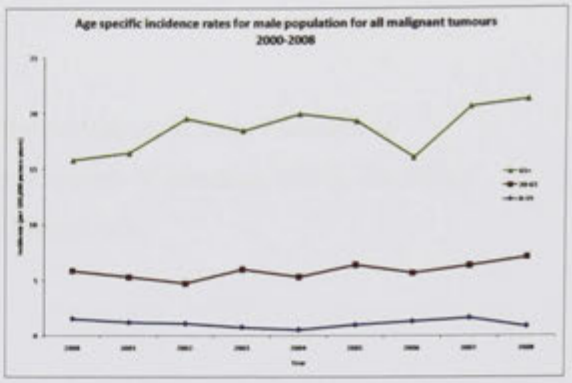
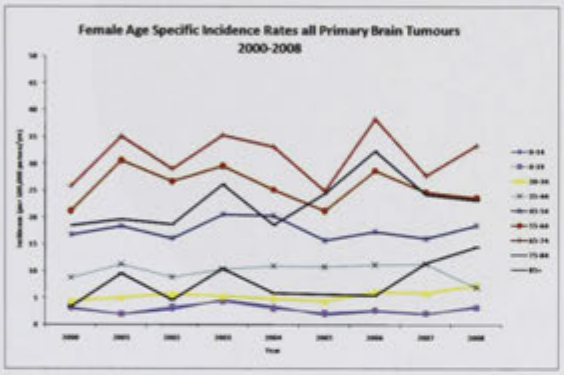


Figure 6.7. c) Age specific incidence rates for male population for all benign tumours, 2000-2008. **d)** Age specific incidence rates for male population for all malignant tumours, 2000-2008.

While incidence rates are similar in younger age groups for both males and females.



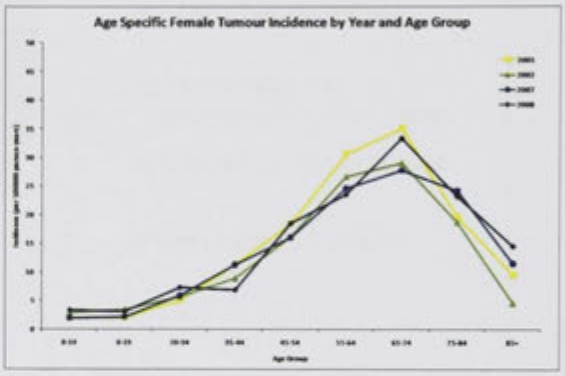
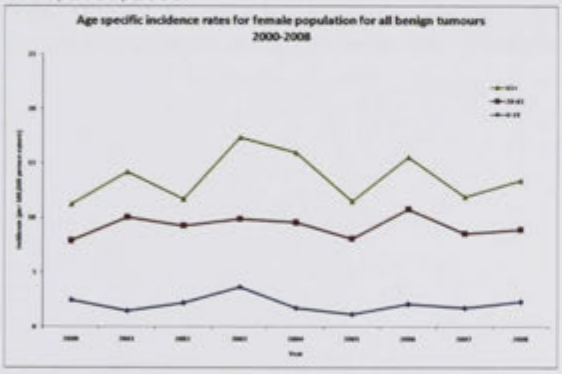


Figure 6.8. a) Age specific incidence rates for female population for all primary brain tumours by year. **b)** Age specific incidence rates for female population for all primary brain tumours with comparison of years 2001, 2002, 2007, 2008.



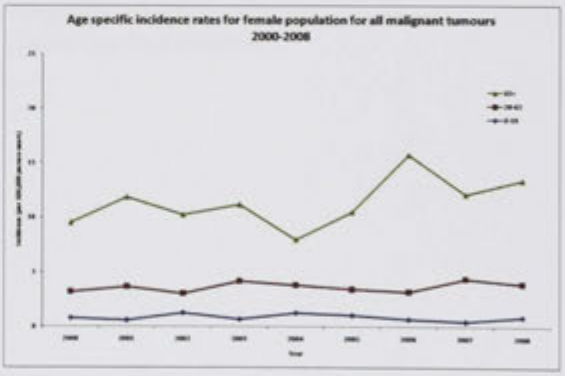


Figure 6.8. c) Age specific incidence rates for female population for all benign tumours, 2000-2008. **d)** Age specific incidence rates for female population for all malignant tumours, 2000-2008.

The majority of primary brain tumours observed in the current study were Tumours of Neuroepithelial Tissue (53%, n = 4024), followed by Tumours of Meninges (26%, n = 1978) and Tumours of the Sellar Region (14%, n = 1036) (**Figure 6.9**).

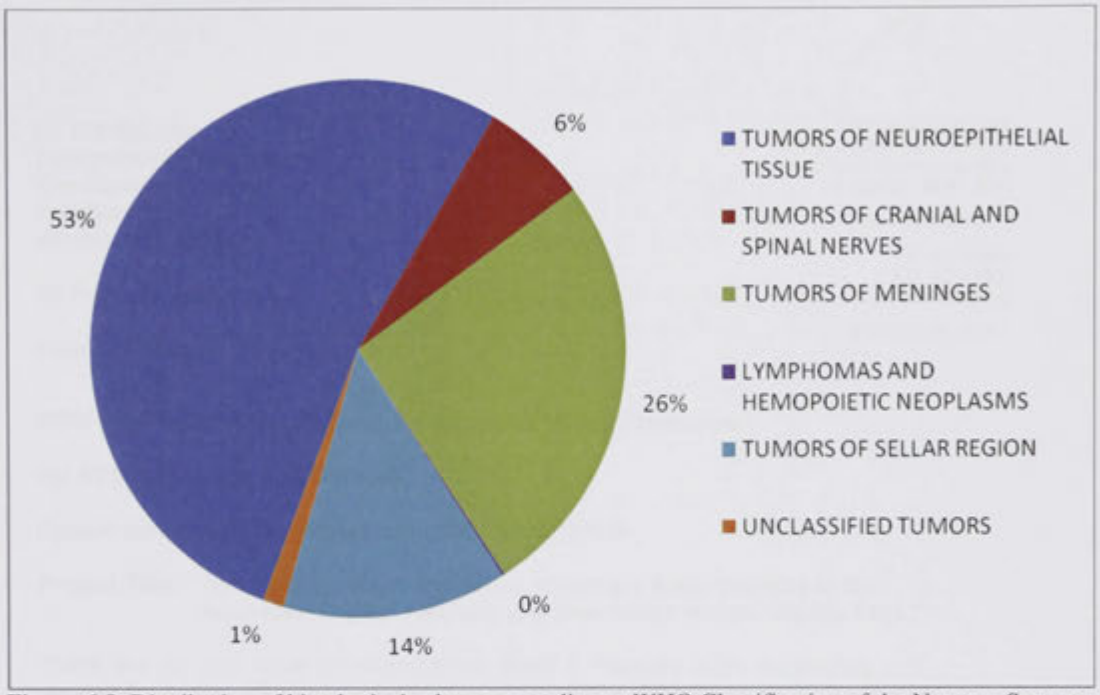


Figure 6.9. Distribution of histological subtype according to WHO Classification of the Nervous System. Percentages are displayed.
Note, although **Figure 6.9** is labelled according to WHO subgroups, no spinal nerve tumours were included in the study as implied by the title "Tumours of Cranial and Spinal nerves".

6.9 *Ethics Approvals*

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23 February 2009

Dear Dr Khurana,

NSW Population & Health Services Research Ethics Committee

AU RED Reference: 08/CIPHS/38

Cancer Institute NSW reference number: 2008/10/099

Project Title: "Temporal trends in incidence of primary brain tumours in the Australian Capital Territory and New South Wales: 1994 to 2008."

Thank you for your email correspondence dated 4 February 2009 responding to a request for further information/clarification of the above referenced study for single ethical and scientific review by the NSW Population & Health Services Research Ethics Committee. The Committee reviewed your response at its meeting held on 19 February 2009 and I am pleased to advise that approval has been granted.

The Committee reviewed and approved the following documents:

- NSW National Ethics Application Form dated 15 September 2008
- Research into Brain Tumours protocol undated
- NSW Privacy form

Approval is valid for the following sites:

- John Hunter Hospital
- Royal North Shore Hospital
- Prince of Wales Hospital
- Wollongong Hospital
- St Vincent's Hospital Darlinghurst
- Concord Repatriation General Hospital
- Liverpool Hospital
- Royal Prince Alfred Hospital
- Nepean Hospital
- Westmead Hospital
- The Children's Hospital at Westmead
- Sydney Adventist Hospital
- Douglass Hanly Moir Pathology, Macquarie Park, Sydney
- Dalcross Private Hospital

Trim Record: E09/03957

The NSW Population & Health Services Research Ethics Committee has been accredited by the NSW Department of Health to provide single ethical and scientific review of research proposals conducted within the NSW public health system.

The Committee is a joint initiative of the Cancer Institute NSW and NSW Department of Health. The Committee has been constituted and operates in accordance with the National Health and Medical Research Council's *National Statement on Ethical Conduct in Human Research (2007)* and relevant legislation and guidelines.

Please note that ethical approval is valid for the duration of the research, conditional on the following:

- Principal investigators will immediately report anything which might warrant a review of ethical approval of the research, including unforeseen events that might affect continued ethical acceptability.
- Proposed amendments to the research proposal or conduct of the research which may affect the ethical acceptability of the research are to be provided to the NSW Population & Health Services Research Ethics Committee for review.
- The NSW Population & Health Services Research Ethics Committee will be notified giving reasons, if the research is discontinued before the expected date of completion.
- The Principal Investigator will provide an annual progress report to the NSW Population & Health Services Research Ethics Committee and at the completion of the study.

For further information about the NSW Population & Health Services Research Ethics Committee please refer to our website www.cancerinstitute.org.au/research.

Should you have any queries about the ethical review of your research proposal please contact the Ethics Coordinator on 02 8374 5600 or email ethics@cancerinstitute.org.au.

The NSW Population & Health Services Research Ethics Committee wishes you well in your research endeavours.

Yours sincerely,

Sharon Falleiro
Ethics Coordinator
Cancer Institute NSW
NSW Population & Health Services Research Ethics Committee

Trim Record: E09/03957

ACT Health Human Research Ethics Committee
Level 3, 11 Moore Street, Canberra City ACT 2601
GPO Box 825 Canberra ACT 2601
Phone: 02 6205 0846 Fax: 02 6205 0842
Website: www.health.act.gov.au
ABN: 82 049 056 234

File No: ETH.6/08.615

Dr Vini Gautam Khurana
Staff Specialist Neurosurgeon
Canberra Hospital
Building 1 Level 9

Dear Dr Khurana

The ACT Health Human Research Ethics Committee considered the proposed study 'Temporal Trends in Incidence of Primary Brain Tumours in the Australian Capital Territory and New South Wales: 1994 to 2008', at the meeting held on 21 July 2008. Ethics Committee Submission No ETH.6/08.615 refers.

The Committee agreed that the application is for low risk research and determined that the research meets the requirements of the National Statement on Ethical Conduct in Human Research and is ethically acceptable.

Please forward a letter of confirmation from the ACT and NSW Cancer Registries to the Committee for its records.

I attach for your records an Outcome of Consideration of Protocol form.

I confirm that the ACT Health Human Research Ethics Committee is constituted according to the National Health and Medical Research Council Guidelines and operates in compliance with applicable regulatory requirements and the International Conference on Harmonization Guidelines on Good Clinical Practice.

You may recall that the ACT Health Guidelines for Submission of Application require you to complete payment of the levy when approved by the Ethics Committee.

Please forward $27.50 levy fee to the Secretariat, ACT Health Human Research Ethics Committee, GPO Box 825, Canberra ACT 2601 as soon as possible. An invoice is attached for your attention.

A copy of your application will be sent to ACT Insurance Authority for consideration. Please note that this may take up to four weeks for more complex matters.

The study cannot commence until you receive written approval from the Insurance and Legal Liaison Manager, Mr Simon Fenton, who can be contacted on (02) 620 50928. Any enquiries regarding insurance matters must be addressed to Mr Fenton.

Yours sincerely

Elizabeth Grant AM, Hon LLD *Monash*
Chair
Ethics Committee

3 August 2008

6.10 References

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